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THE BRIGHAM BOARD REVIEW IN CRITICAL CARE MEDICINE

from BWH BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Affiliate of Harvard Medical School

The Brigham Board Review in Critical Care Medicine
Presented by: Brigham and Women's Hospital
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- Identify and Apply current therapeutic options for specific critical care disorders;
- Analyze and Interpret up-to-date literature relevant to clinical practice in critical care medicine;
- Recognize and Apply knowledge of pathophysiology as it applies to management of critical care disorders;
- Apply knowledge gained to the ABIM certification/recertification critical care examinations

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The Brigham Board Review in Critical Care Medicine

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SHOCK

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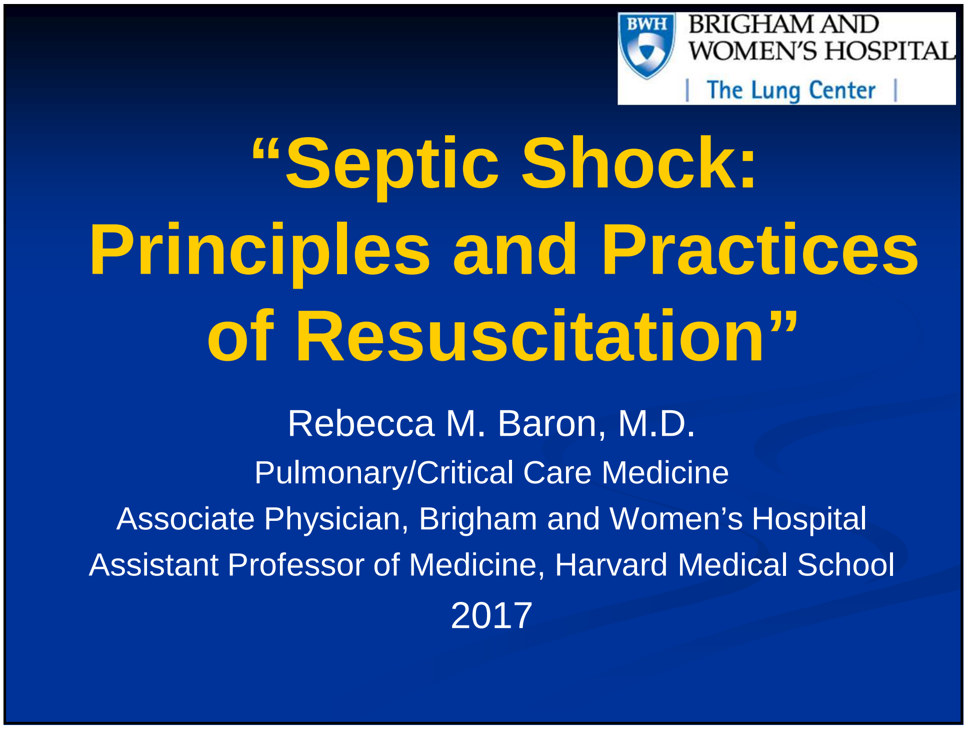

BRIGHAM AND WOMEN'S HOSPITAL | The Lung Center |

"Septic Shock: Principles and Practices of Resuscitation"

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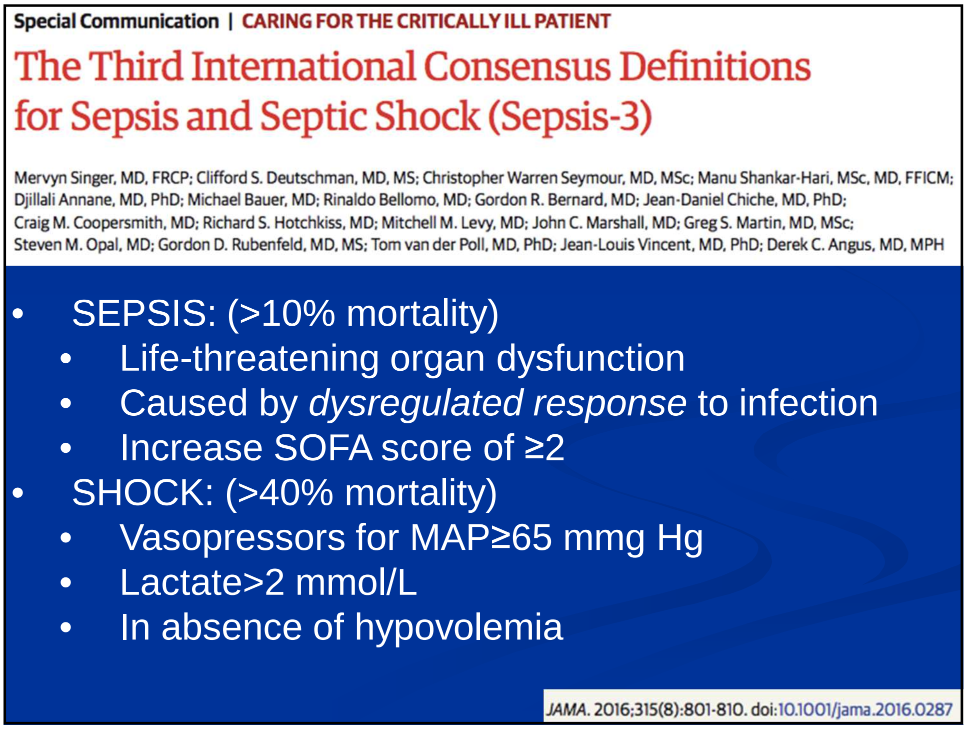
2017

Disclosures: None



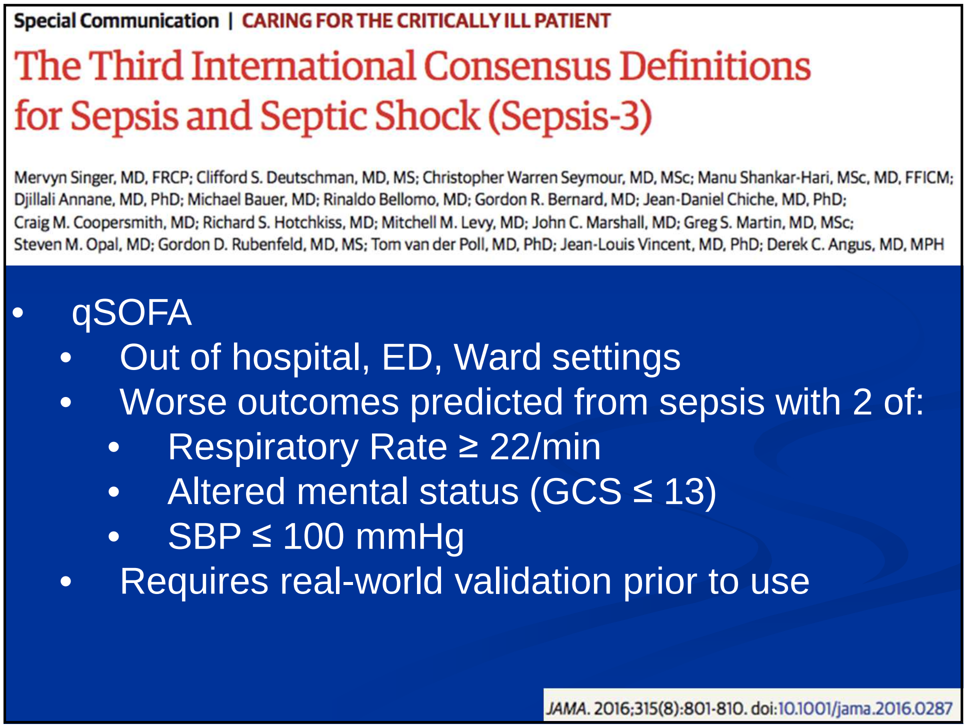
Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

- SEPSIS: (>10% mortality)
  - Life-threatening organ dysfunction
  - Caused by *dysregulated response* to infection
  - Increase SOFA score of ≥2
- SHOCK: (>40% mortality)
  - Vasopressors for MAP≥65 mmg Hg
  - Lactate>2 mmol/L
  - In absence of hypovolemia

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287



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- qSOFA
  - Out of hospital, ED, Ward settings
  - Worse outcomes predicted from sepsis with 2 of:
    - Respiratory Rate ≥ 22/min
    - Altered mental status (GCS ≤ 13)
    - SBP ≤ 100 mmHg
  - Requires real-world validation prior to use

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

What about fluid resuscitation?

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

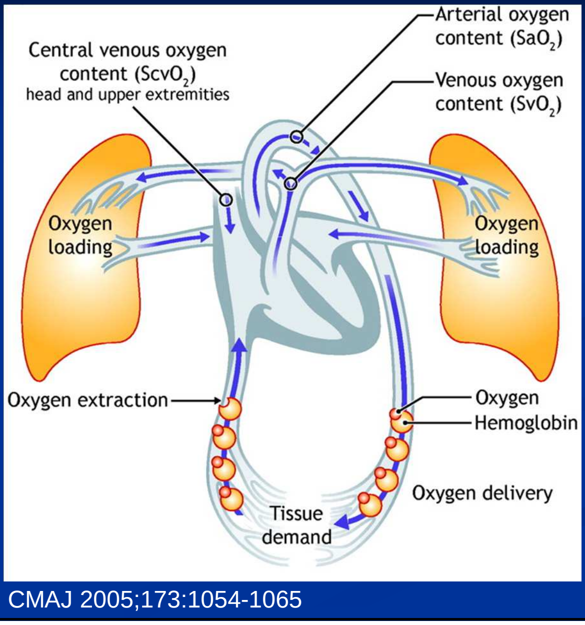
*Treatment began in E.D.: 6-hours

*A-line, Central line insertion

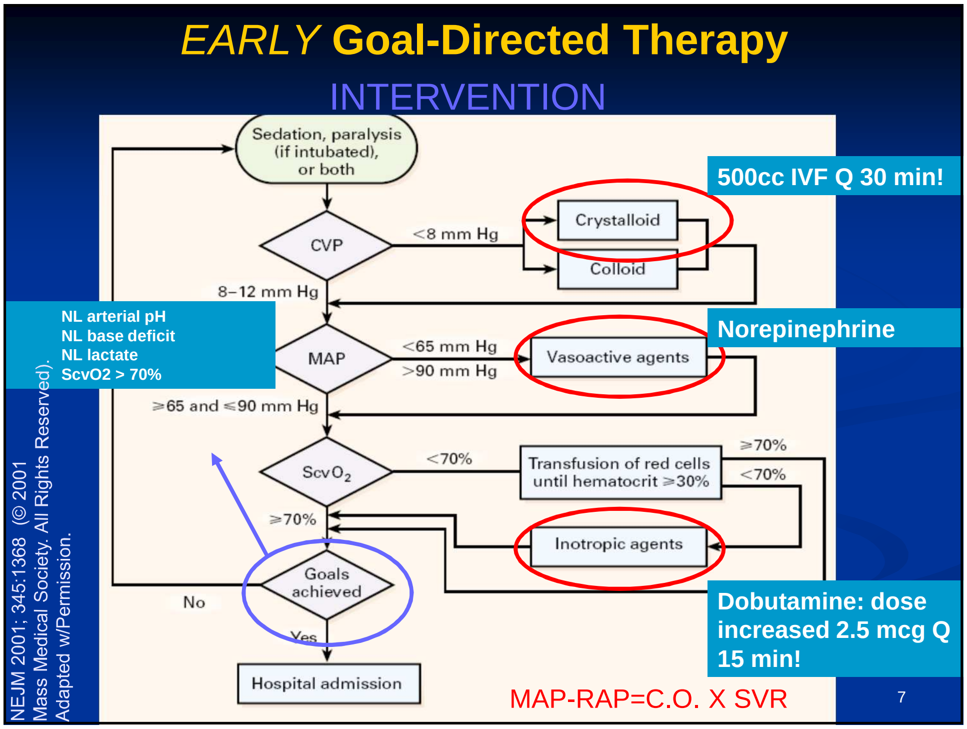
*Monitored: Mean arterial BP (MAP)
Central venous pressure (CVP)
Central venous O2 sat ($S_{CV}O_2$)
Hematocrit

NEJM 2001; 345:1368

Oxygen Supply vs. Demand


Arterial oxygen content (SaO_2)
Central venous oxygen content ($ScvO_2$)
head and upper extremities
Venous oxygen content (SvO_2)
Oxygen loading
Oxygen loading
Oxygen extraction
Oxygen
Hemoglobin
Oxygen delivery
Tissue demand

Rivers, E. P. et al. CMAJ 2005;173:1054-1065



EARLY Goal-Directed Therapy

INTERVENTION

Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO₂
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

500cc IVF Q 30 min!

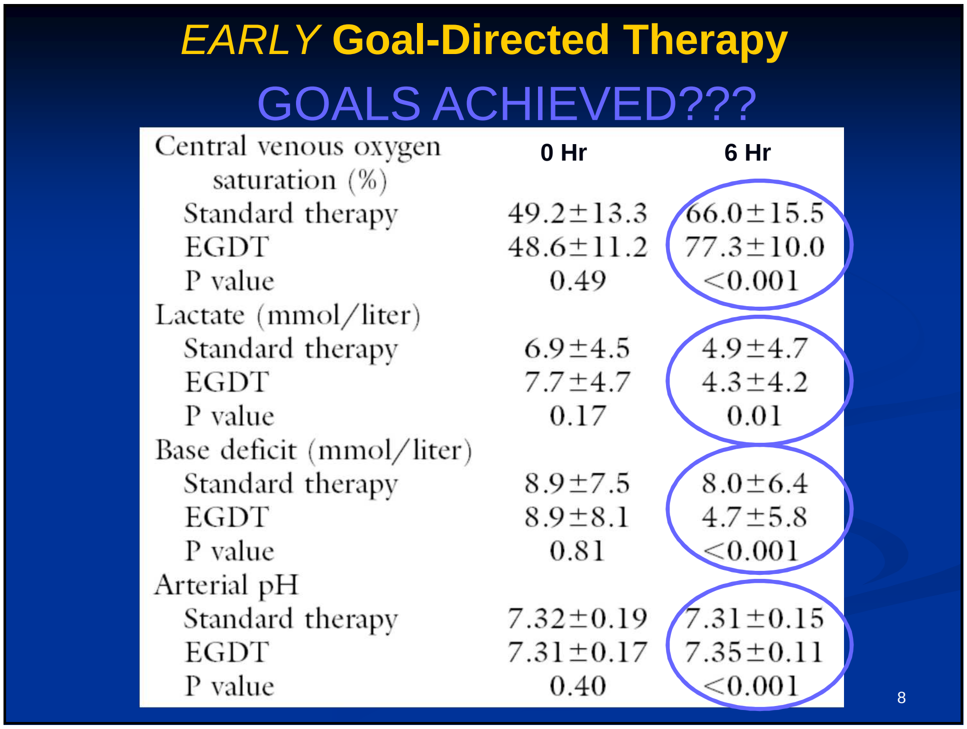
Norepinephrine

NL arterial pH
NL base deficit
NL lactate
ScvO2 > 70%

Dobutamine: dose increased 2.5 mcg Q 15 min!

MAP-RAP=C.O. X SVR

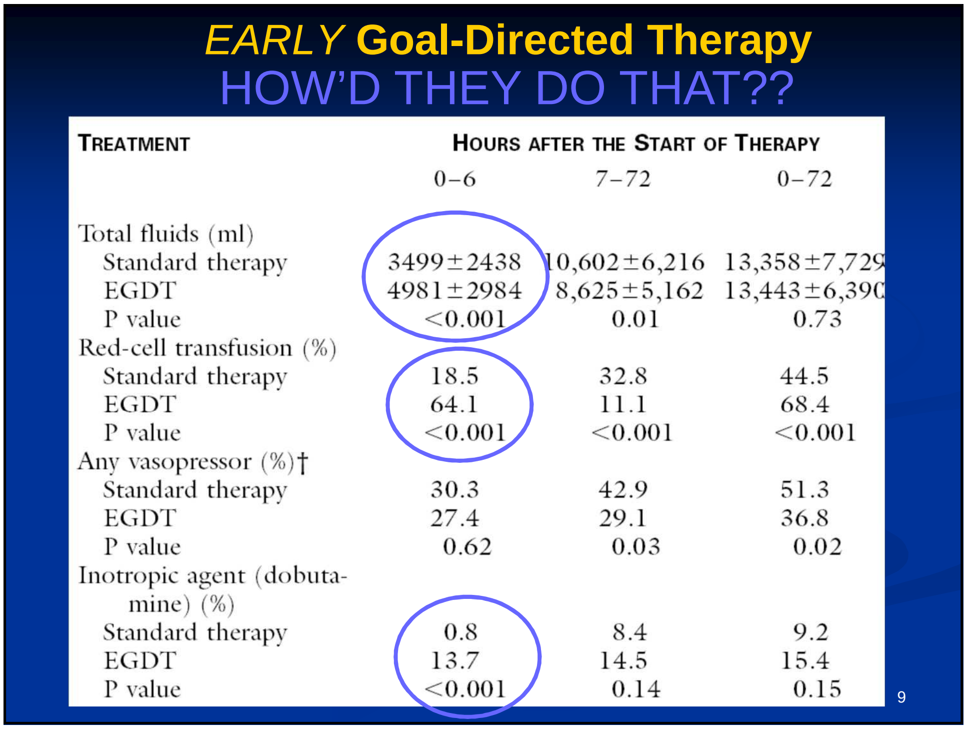
NEJM 2001; 345:1368 (© 2001 Mass Medical Society. All Rights Reserved).
Adapted w/Permission.



EARLY Goal-Directed Therapy

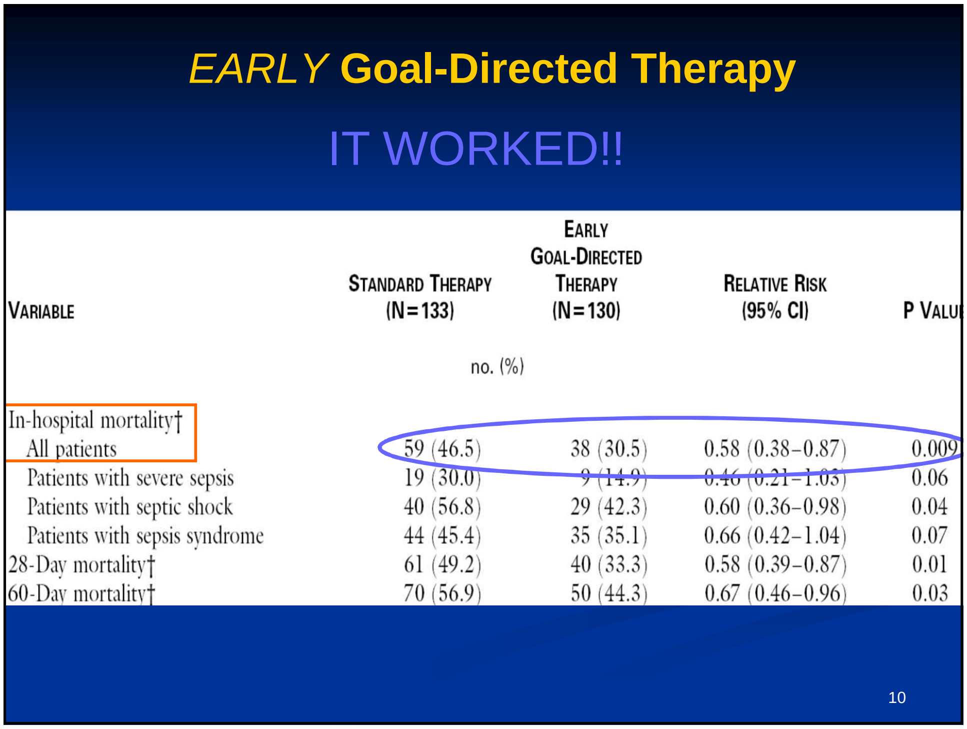
GOALS ACHIEVED???

	0 Hr	6 Hr
Central venous oxygen saturation (%)		
Standard therapy	49.2±13.3	66.0±15.5
EGDT	48.6±11.2	77.3±10.0
P value	0.49	<0.001
Lactate (mmol/liter)		
Standard therapy	6.9±4.5	4.9±4.7
EGDT	7.7±4.7	4.3±4.2
P value	0.17	0.01
Base deficit (mmol/liter)		
Standard therapy	8.9±7.5	8.0±6.4
EGDT	8.9±8.1	4.7±5.8
P value	0.81	<0.001
Arterial pH		
Standard therapy	7.32±0.19	7.31±0.15
EGDT	7.31±0.17	7.35±0.11
P value	0.40	<0.001



EARLY Goal-Directed Therapy
HOW'D THEY DO THAT??

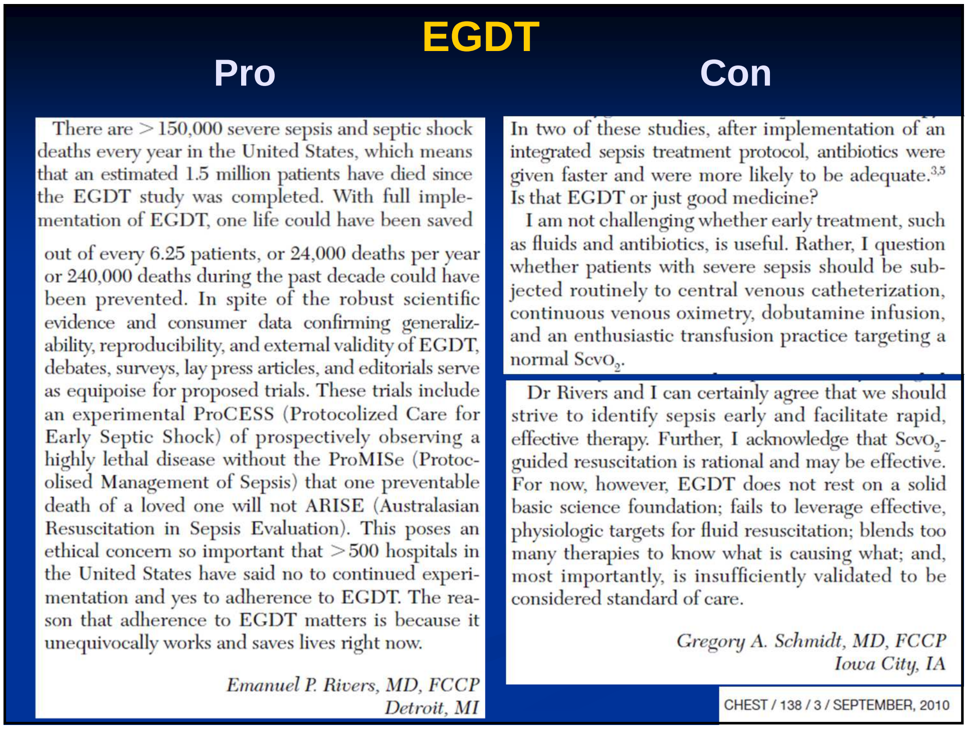
TREATMENT	HOURS AFTER THE START OF THERAPY		
	0–6	7–72	0–72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15



EARLY Goal-Directed Therapy

IT WORKED!!

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALU
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03



EGDT

Pro

There are >150,000 severe sepsis and septic shock deaths every year in the United States, which means that an estimated 1.5 million patients have died since the EGDT study was completed. With full implementation of EGDT, one life could have been saved out of every 6.25 patients, or 24,000 deaths per year or 240,000 deaths during the past decade could have been prevented. In spite of the robust scientific evidence and consumer data confirming generalizability, reproducibility, and external validity of EGDT, debates, surveys, lay press articles, and editorials serve as equipoise for proposed trials. These trials include an experimental ProCESS (Protocolized Care for Early Septic Shock) of prospectively observing a highly lethal disease without the ProMISe (Protocolised Management of Sepsis) that one preventable death of a loved one will not ARISE (Australasian Resuscitation in Sepsis Evaluation). This poses an ethical concern so important that >500 hospitals in the United States have said no to continued experimentation and yes to adherence to EGDT. The reason that adherence to EGDT matters is because it unequivocally works and saves lives right now.

Emanuel P. Rivers, MD, FCCP
Detroit, MI

Con

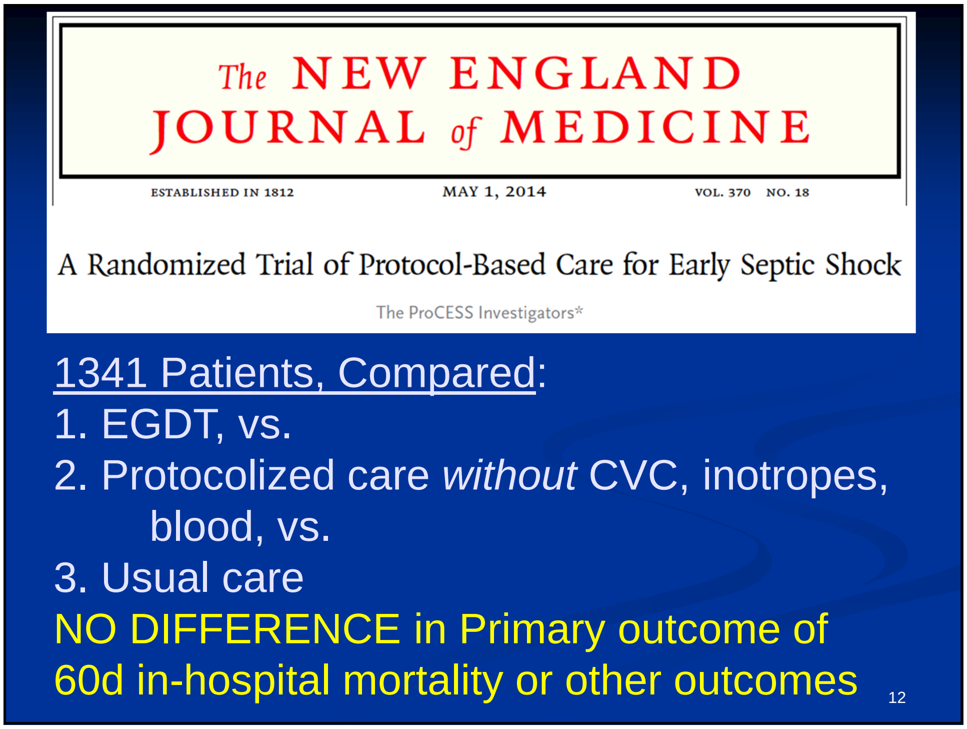
In two of these studies, after implementation of an integrated sepsis treatment protocol, antibiotics were given faster and were more likely to be adequate.[3,5] Is that EGDT or just good medicine?

I am not challenging whether early treatment, such as fluids and antibiotics, is useful. Rather, I question whether patients with severe sepsis should be subjected routinely to central venous catheterization, continuous venous oximetry, dobutamine infusion, and an enthusiastic transfusion practice targeting a normal $ScvO_2$.

Dr Rivers and I can certainly agree that we should strive to identify sepsis early and facilitate rapid, effective therapy. Further, I acknowledge that $ScvO_2$-guided resuscitation is rational and may be effective. For now, however, EGDT does not rest on a solid basic science foundation; fails to leverage effective, physiologic targets for fluid resuscitation; blends too many therapies to know what is causing what; and, most importantly, is insufficiently validated to be considered standard of care.

Gregory A. Schmidt, MD, FCCP
Iowa City, IA

CHEST / 138 / 3 / SEPTEMBER, 2010



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

1341 Patients, Compared:

1. EGDT, vs.
2. Protocolized care *without* CVC, inotropes, blood, vs.
3. Usual care

NO DIFFERENCE in Primary outcome of 60d in-hospital mortality or other outcomes

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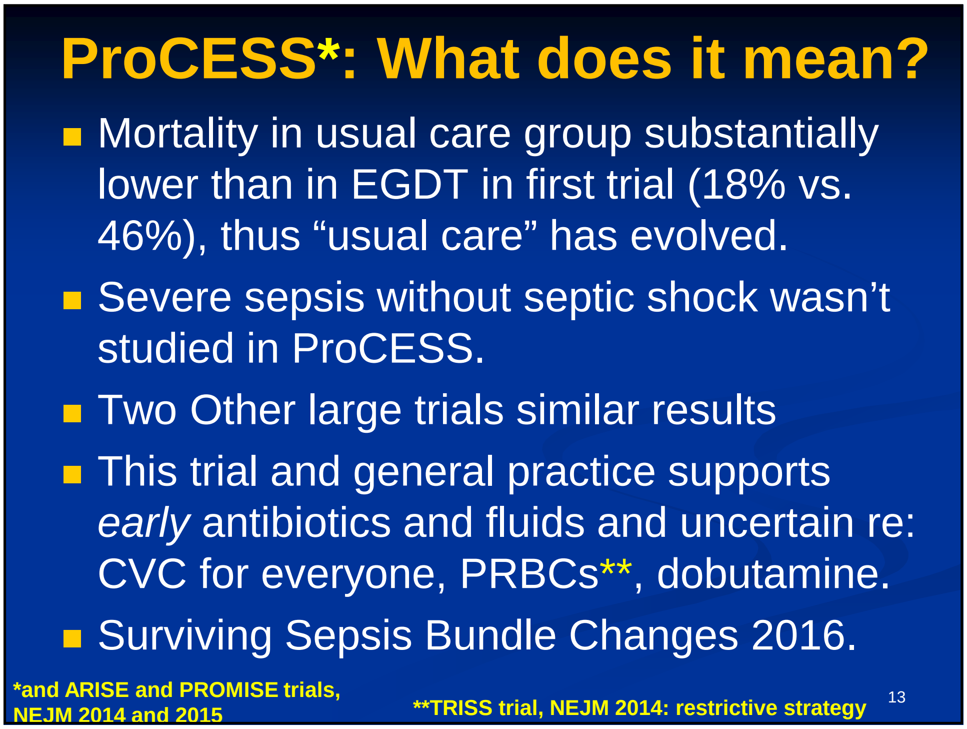
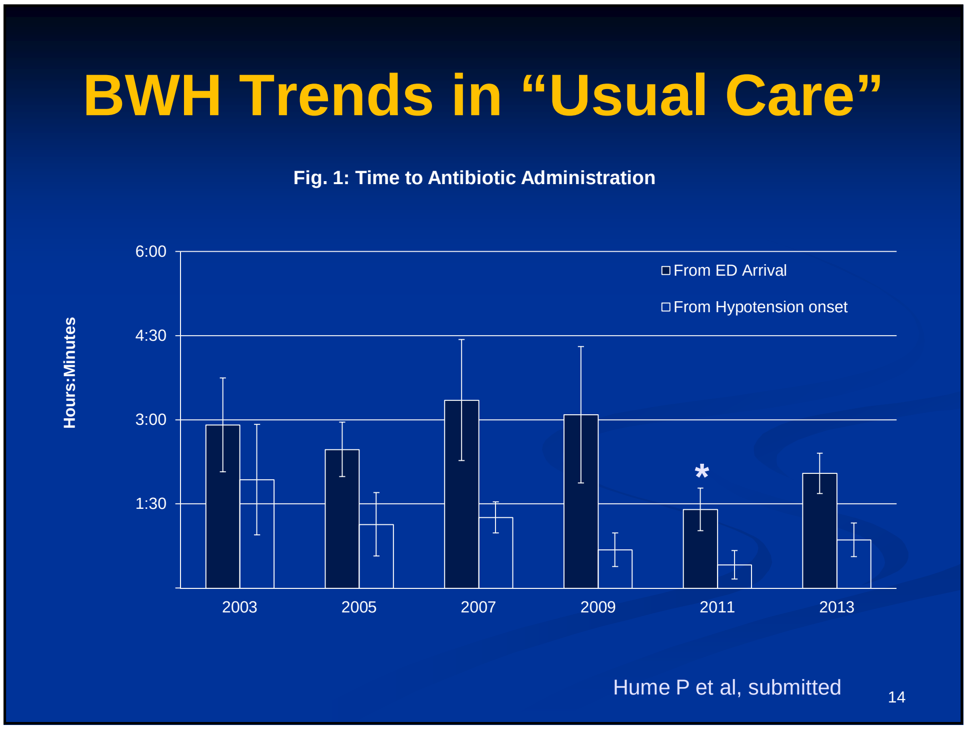


ProCESS*: What does it mean?

- Mortality in usual care group substantially lower than in EGDT in first trial (18% vs. 46%), thus “usual care” has evolved.
- Severe sepsis without septic shock wasn’t studied in ProCESS.
- Two Other large trials similar results
- This trial and general practice supports *early* antibiotics and fluids and uncertain re: CVC for everyone, PRBCs**, dobutamine.
- Surviving Sepsis Bundle Changes 2016.

***and ARISE and PROMISE trials, NEJM 2014 and 2015**

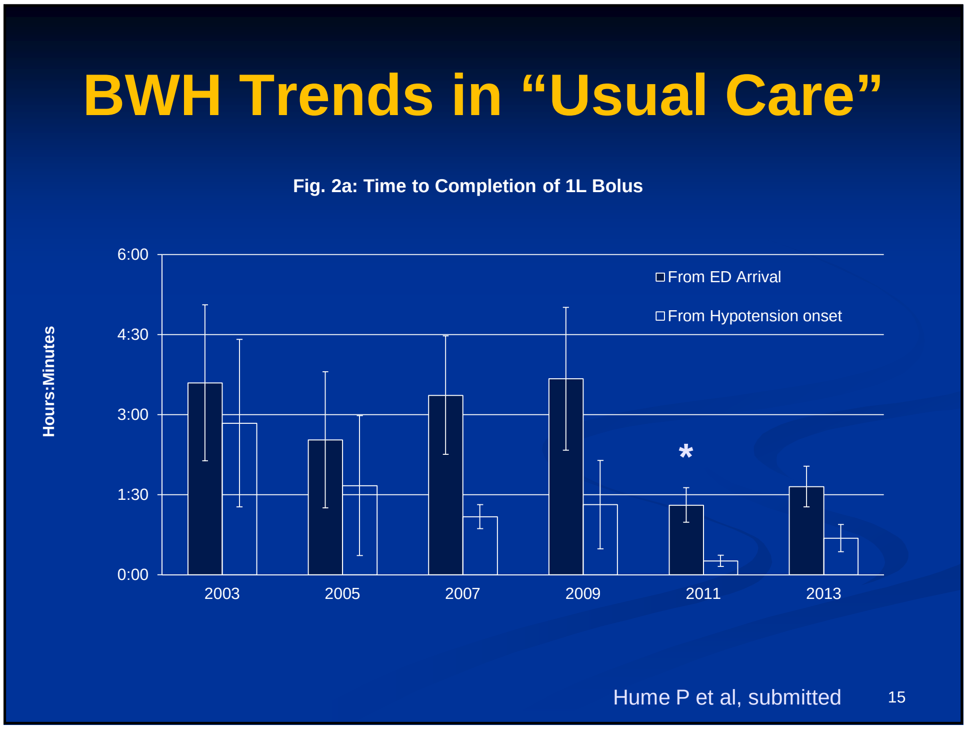
****TRISS trial, NEJM 2014: restrictive strategy**



BWH Trends in “Usual Care”

Fig. 1: Time to Antibiotic Administration

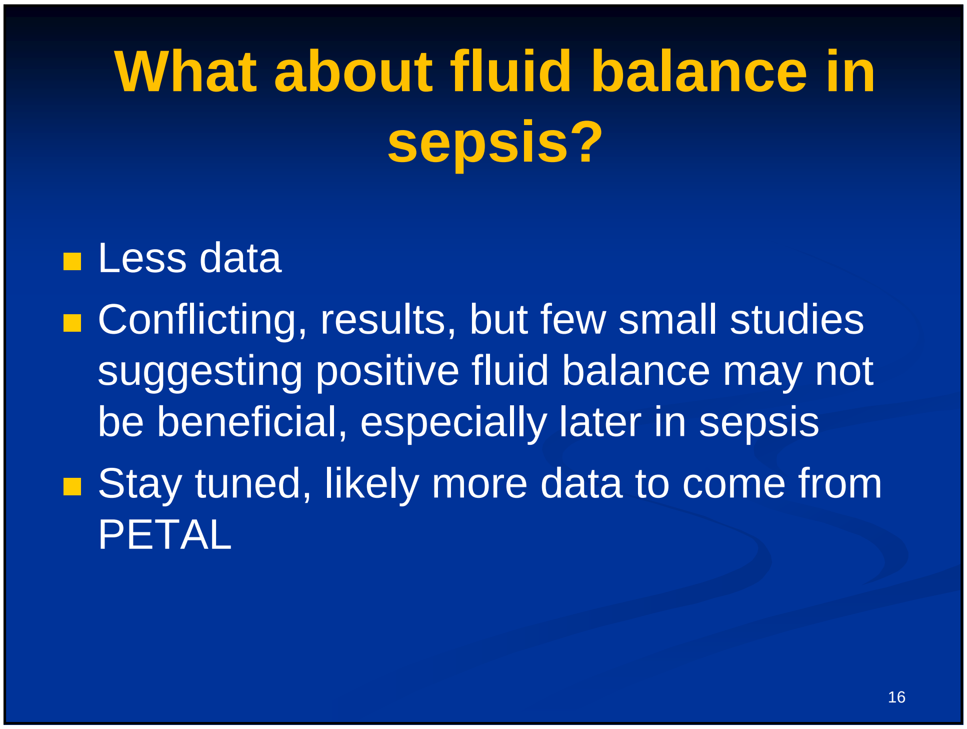
Hume P et al, submitted



BWH Trends in "Usual Care"

Fig. 2a: Time to Completion of 1L Bolus

Hume P et al, submitted



What about fluid balance in sepsis?

- Less data
- Conflicting, results, but few small studies suggesting positive fluid balance may not be beneficial, especially later in sepsis
- Stay tuned, likely more data to come from PETAL

Infection

Toxin, Molecular Signaling Paths

Host Response

*Inflammation

Vasodilatation

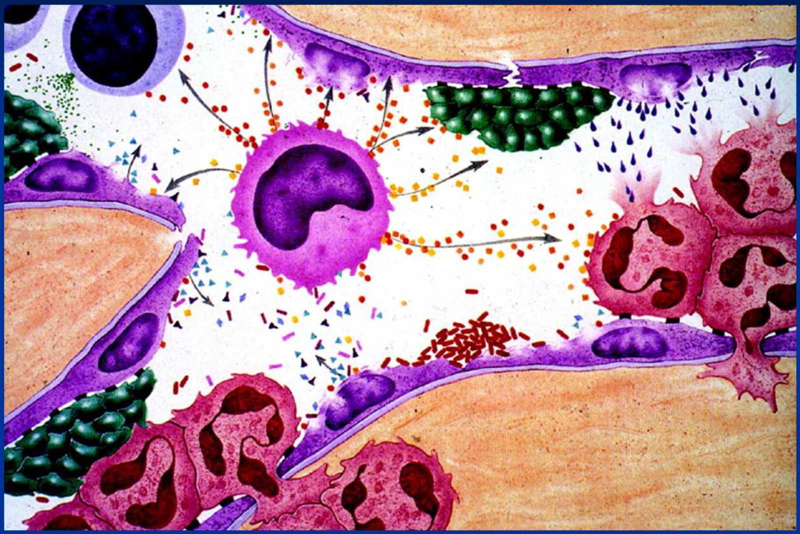
Myocardial Depression

Tissue Microthrombosis

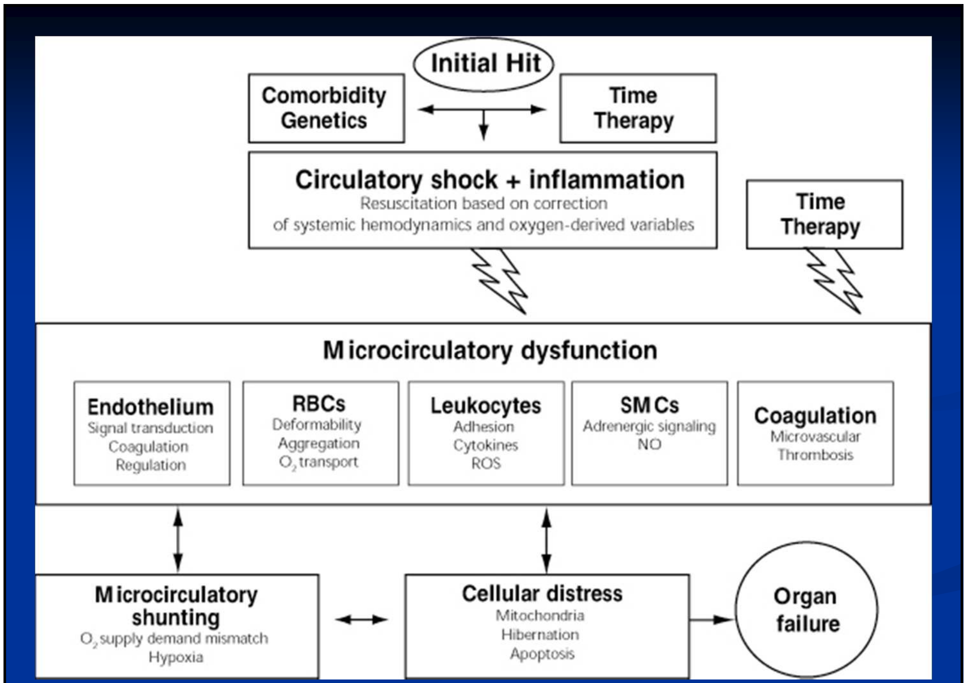
Neuroendocrine Effects

*Initially, later anti-inflammatory host response

From Macro- to Microcirculation



Rivers, E. P. et al. CMAJ 2005;173:1054-1065

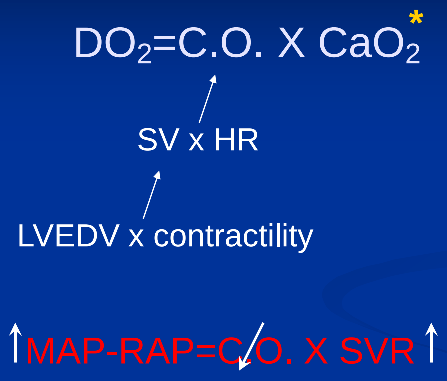

Initial Hit
Comorbidity
Genetics
Time
Therapy
Circulatory shock + inflammation
Resuscitation based on correction
of systemic hemodynamics and oxygen-derived variables
Time
Therapy
Microcirculatory dysfunction
Endothelium
Signal transduction
Coagulation
Regulation
RBCs
Deformability
Aggregation
O₂ transport
Leukocytes
Adhesion
Cytokines
ROS
SMCs
Adrenergic signaling
NO
Coagulation
Microvascular
Thrombosis
Microcirculatory
shunting
O₂ supply demand mismatch
Hypoxia
Cellular distress
Mitochondria
Hibernation
Apoptosis
Organ
failure

Crit Care 2005; 9(Suppl 4):S13

Sepsis: Source Control

- EARLY (1h), BROAD, EMPIRIC antibiotic therapy
  - Not the time to be elegant!
- Think of sources needing SURGICAL INTERVENTION
  - Catheter / device → Remove it
  - Soft tissue abscess → Drain it
  - Empyema → Chest tube
  - Cholangitis → ERCP
  - Endocarditis → Abx/Valve replacement
  - Septic arthritis → Joint debridement
- Narrow therapy after 48 – 72H of cultures

"Fill the Tank"



DO_2=C.O. X CaO_2*

SV x HR

LVEDV x contractility

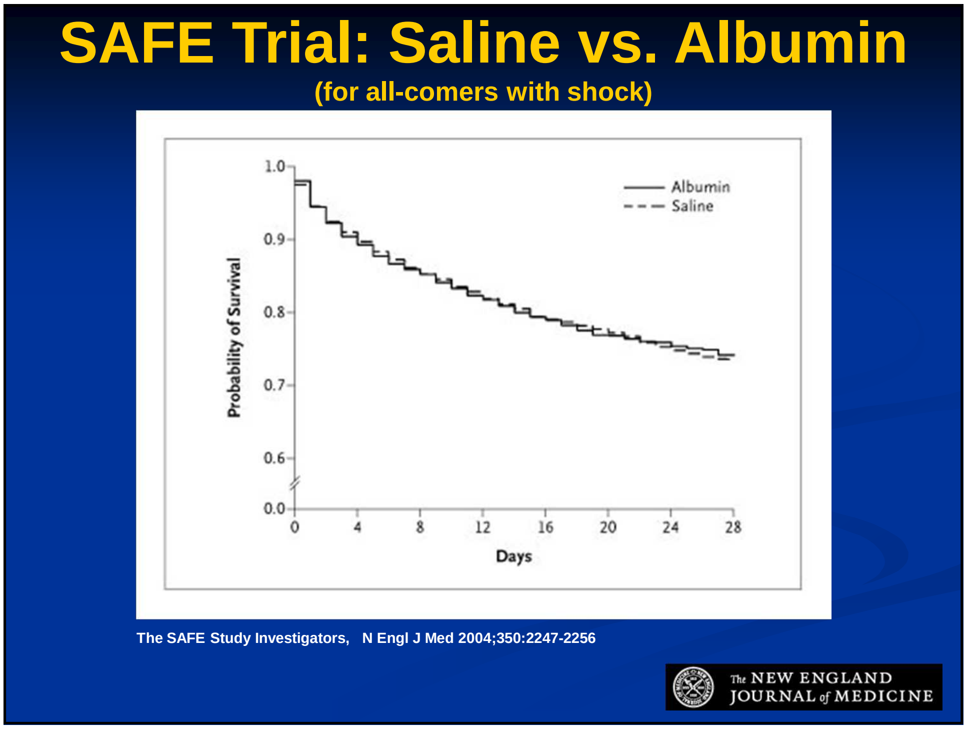
↑MAP-RAP=C.O. X SVR↑

* CaO2 = 1.34 x Hgb x SaO2

What type of volume resuscitation: crystalloid vs. colloid?

- Must restore intravascular volume
- Need rapid & aggressive use of crystalloid vs. colloid
- Deliver as bolus infusion (via 2 large-bore iv's and/or Cordis)
- Avoid use of vasopressors as will potentially exacerbate tissue hypoxia
- Treat the underlying problem

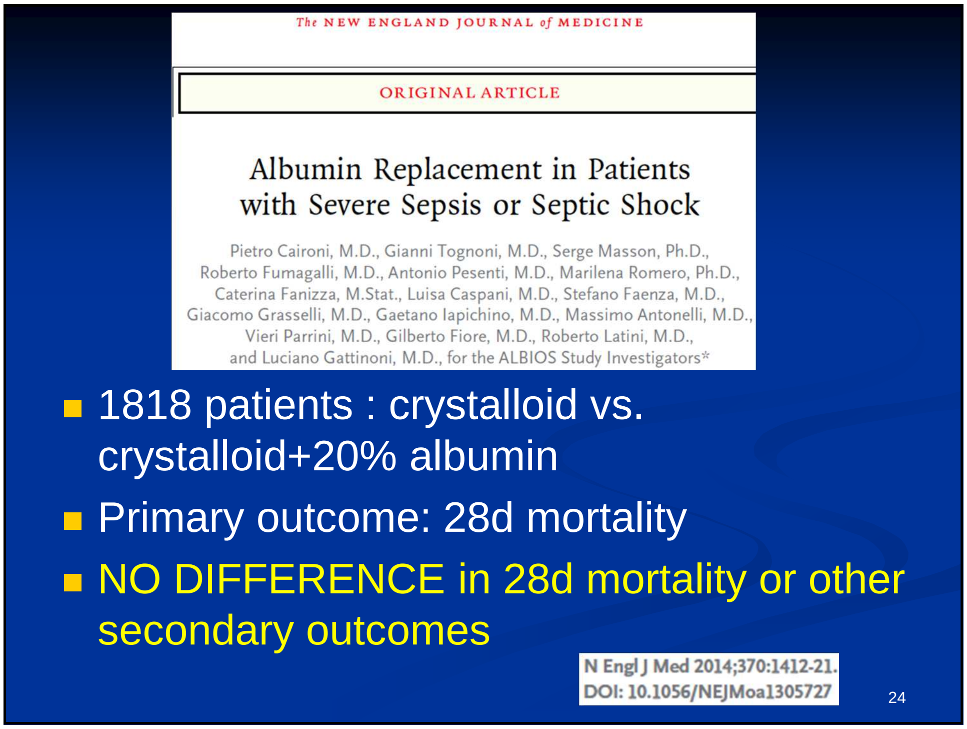
SAFE Study, NEJM 2004; 350:2247.



SAFE Trial: Saline vs. Albumin

(for all-comers with shock)

The SAFE Study Investigators, N Engl J Med 2004;350:2247-2256



The NEW ENGLAND JOURNAL of MEDICINE

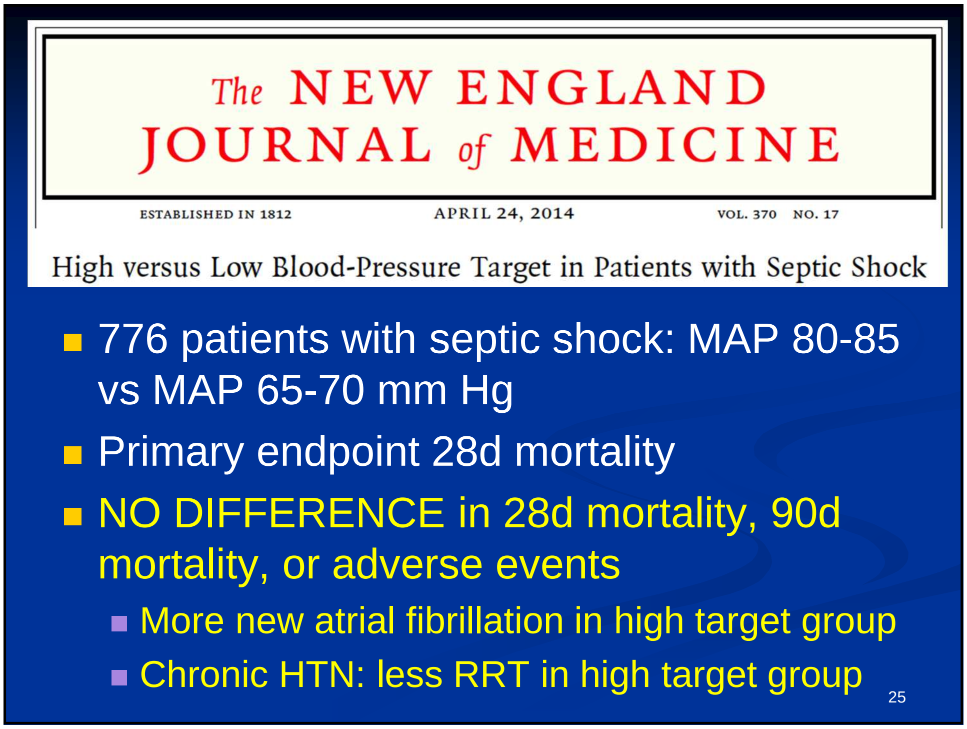
ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D.,
Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D.,
Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D.,
Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D.,
Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D.,
and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

- 1818 patients : crystalloid vs. crystalloid+20% albumin
- Primary outcome: 28d mortality
- NO DIFFERENCE in 28d mortality or other secondary outcomes

N Engl J Med 2014;370:1412-21.
DOI: 10.1056/NEJMoa1305727

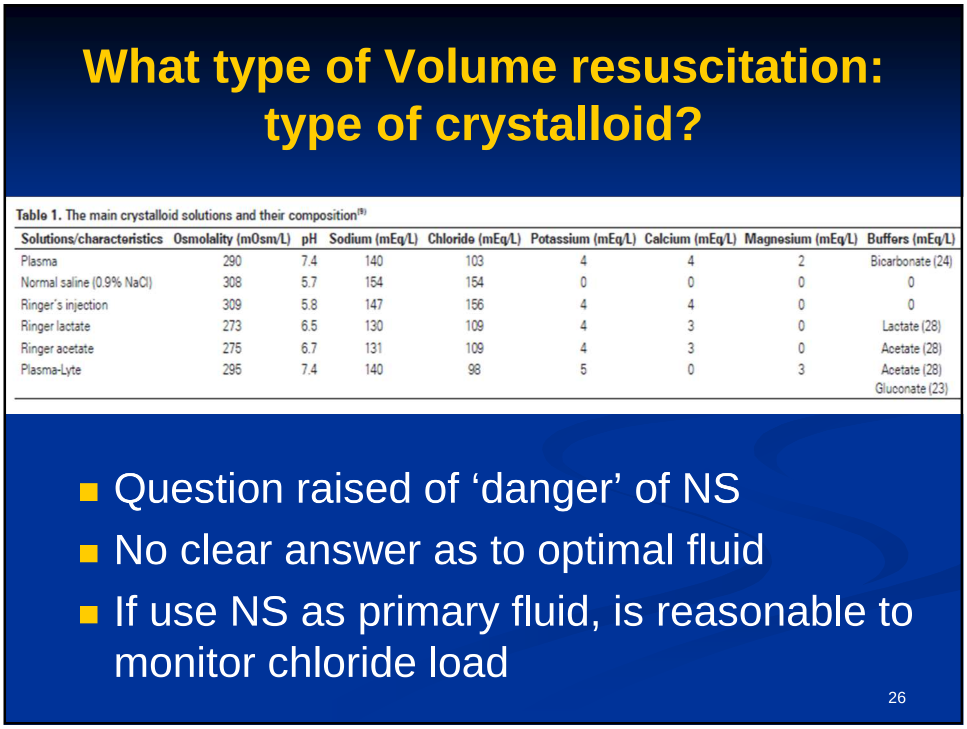


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

High versus Low Blood-Pressure Target in Patients with Septic Shock

- 776 patients with septic shock: MAP 80-85 vs MAP 65-70 mm Hg
- Primary endpoint 28d mortality
- NO DIFFERENCE in 28d mortality, 90d mortality, or adverse events
  - More new atrial fibrillation in high target group
  - Chronic HTN: less RRT in high target group

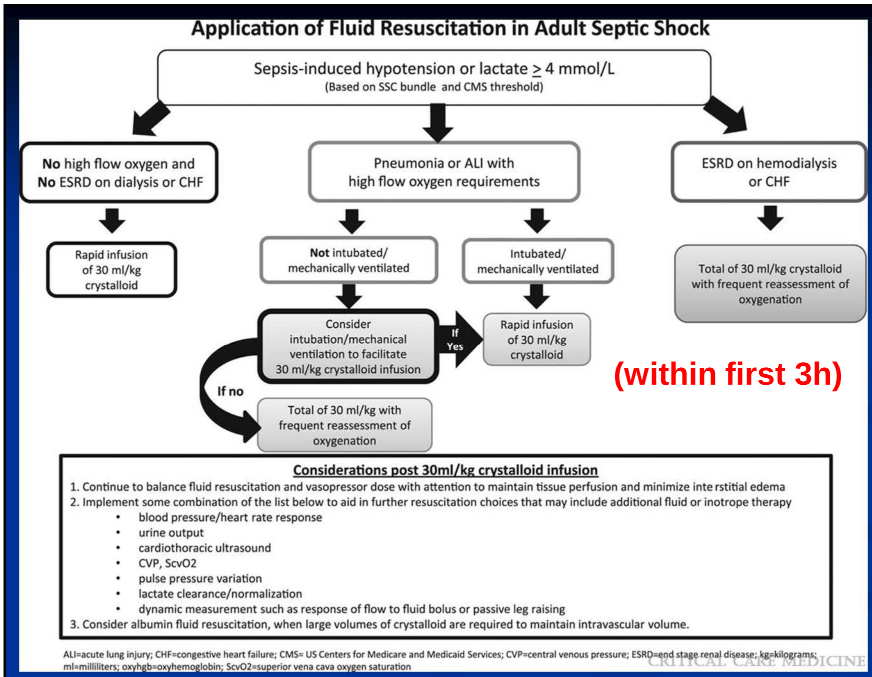


What type of Volume resuscitation: type of crystalloid?

Table 1. The main crystalloid solutions and their composition[9]

Solutions/characteristics	Osmolality (mOsm/L)	pH	Sodium (mEq/L)	Chloride (mEq/L)	Potassium (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Buffers (mEq/L)
Plasma	290	7.4	140	103	4	4	2	Bicarbonate (24)
Normal saline (0.9% NaCl)	308	5.7	154	154	0	0	0	0
Ringer's injection	309	5.8	147	156	4	4	0	0
Ringer lactate	273	6.5	130	109	4	3	0	Lactate (28)
Ringer acetate	275	6.7	131	109	4	3	0	Acetate (28)
Plasma-Lyte	295	7.4	140	98	5	0	3	Acetate (28) Gluconate (23)

- Question raised of 'danger' of NS
- No clear answer as to optimal fluid
- If use NS as primary fluid, is reasonable to monitor chloride load



Application of Fluid Resuscitation in Adult Septic Shock

Sepsis-induced hypotension or lactate ≥ 4 mmol/L
(Based on SSC bundle and CMS threshold)

No high flow oxygen and **No** ESRD on dialysis or CHF

Rapid infusion of 30 ml/kg crystalloid

Pneumonia or ALI with high flow oxygen requirements

Not intubated/ mechanically ventilated

Consider intubation/mechanical ventilation to facilitate 30 ml/kg crystalloid infusion

If Yes

If no

Total of 30 ml/kg with frequent reassessment of oxygenation

Intubated/ mechanically ventilated

Rapid infusion of 30 ml/kg crystalloid

ESRD on hemodialysis or CHF

Total of 30 ml/kg crystalloid with frequent reassessment of oxygenation

(within first 3h)

Considerations post 30ml/kg crystalloid infusion

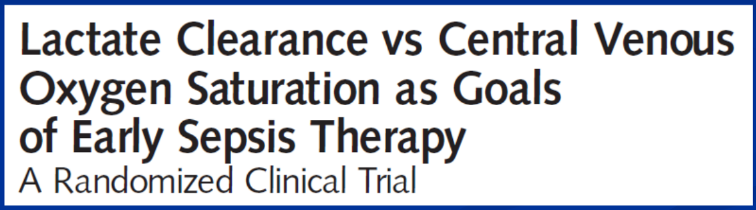
1. Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize interstitial edema
2. Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy
    - blood pressure/heart rate response
    - urine output
    - cardiothoracic ultrasound
    - CVP, ScvO2
    - pulse pressure variation
    - lactate clearance/normalization
    - dynamic measurement such as response of flow to fluid bolus or passive leg raising
3. Consider albumin fluid resuscitation, when large volumes of crystalloid are required to maintain intravascular volume.

ALI=acute lung injury; CHF=congestive heart failure; CMS= US Centers for Medicare and Medicaid Services; CVP=central venous pressure; ESRD=end stage renal disease; kg=kilograms; ml=milliliters; oxyhgb=oxyhemoglobin; ScvO2=superior vena cava oxygen saturation

CRITICAL CARE MEDICINE

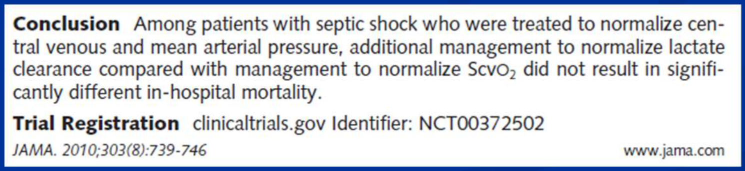
Surviving Sepsis Guidelines 2016, ICM 2017

CMS guideline: Baseline lactate, then if elevated again at 6h



Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

A Randomized Clinical Trial

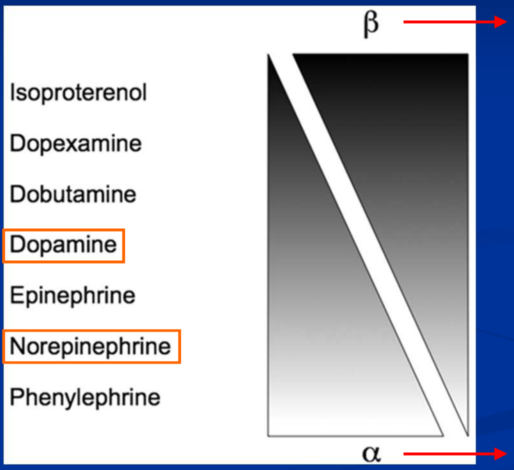


Conclusion Among patients with septic shock who were treated to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance compared with management to normalize $ScvO_2$ did not result in significantly different in-hospital mortality.

Trial Registration clinicaltrials.gov Identifier: NCT00372502

JAMA. 2010;303(8):739-746 www.jama.com

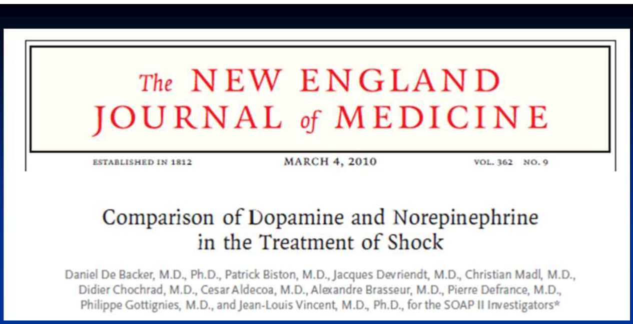
Action of Vasoactive Catecholamines


β
Isoproterenol
Dopexamine
Dobutamine
Dopamine
Epinephrine
Norepinephrine
Phenylephrine
α

β1: HR, Contractility
β2: Vasodilation

Vasoconstriction

Chest 2007; 132:1678-1687



The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

Comparison of Dopamine and Norepinephrine
in the Treatment of Shock

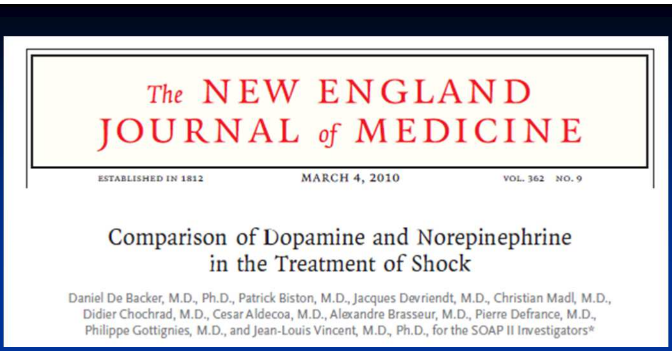
Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D.,
Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D.,
Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

Multi-center, RCT, 1679 patients with shock
(858 patients→DA; 821→NE)

Primary endpoint: 28d Mortality

↓

No Significant Difference
(DA: 52.5%, NE: 48.5%)



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ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

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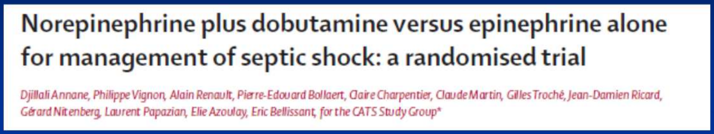
Secondary and Subgroup Analyses:

1. DA→Increased arrhythmias
2. DA→Increased 28d mortality in cardiogenic shock subgroup

Epinephrine as 2^{nd}-line Pressor (after Norepinephrine)



Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

Djillali Annane, Philippe Vignon, Alain Renault, Pierre-Edouard Bollaert, Claire Charpentier, Claude Martin, Gilles Troché, Jean-Damien Ricard, Gérard Nitenberg, Laurent Papazian, Elie Azoulay, Eric Bellissant, for the CATS Study Group*

330 Patients with Septic Shock:
NE + Dobut (if needed) vs. Epi

Primary Outcome: 28d Mortality

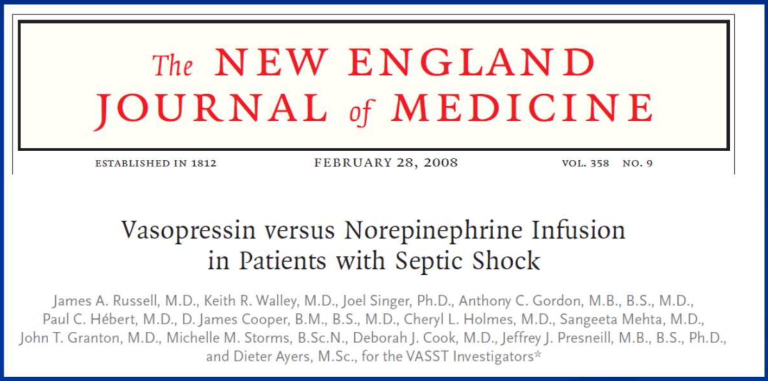
↓

No Difference

Similar secondary outcomes and adverse events rates, as well

Lancet 2007; 370: 676–84

“Vasopressin Deficiency” in Sepsis?



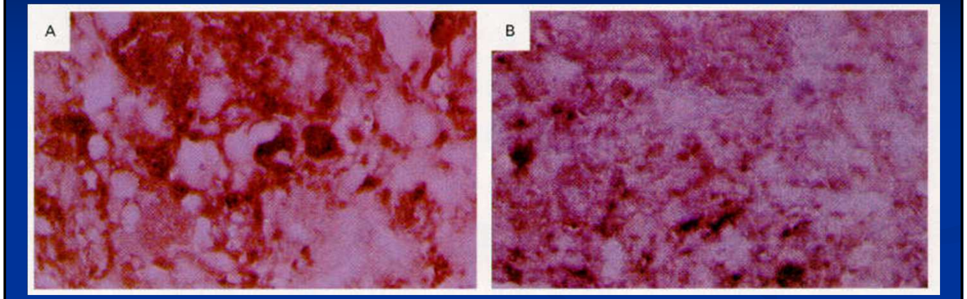
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2008 VOL. 358 NO. 9

Vasopressin versus Norepinephrine Infusion
in Patients with Septic Shock

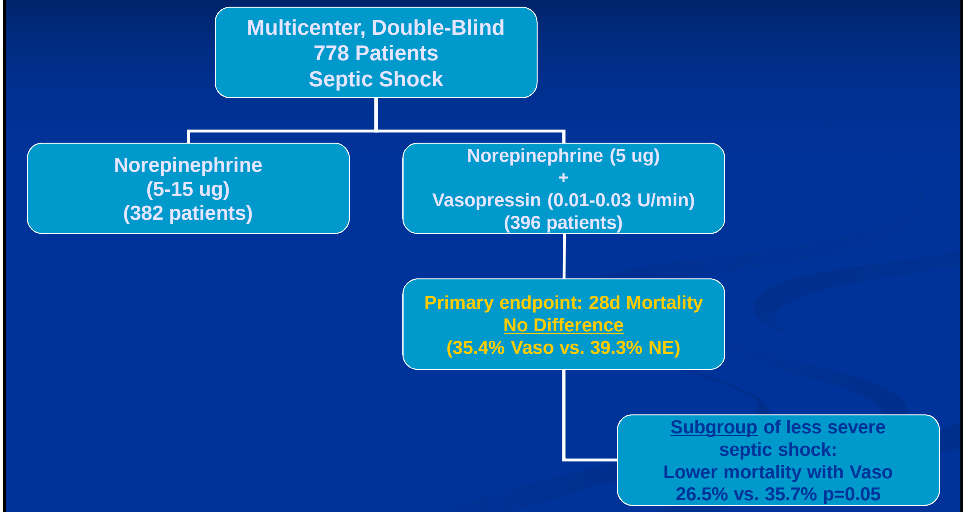
James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D.,
Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D.,
John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D.,
and Dieter Ayers, M.Sc., for the VASST Investigators*

Vasopressin Depletion



- Figure A- section of neurohypophysis from normal dog stained w/ antivasopressin serum
- Figure B- Dog after severe hemorrhagic hypotension (MAP < 40 x 1 hour)

Norepinephrine *vs.* NE+Vasopressin


Multicenter, Double-Blind
778 Patients
Septic Shock

Norepinephrine
(5-15 ug)
(382 patients)

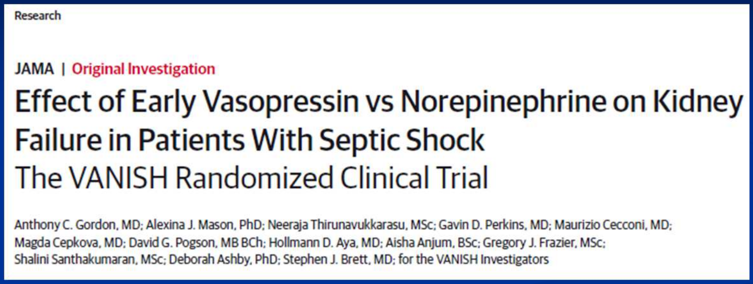
Norepinephrine (5 ug)
+
Vasopressin (0.01-0.03 U/min)
(396 patients)

Primary endpoint: 28d Mortality
No Difference
(35.4% Vaso vs. 39.3% NE)

Subgroup of less severe
septic shock:
Lower mortality with Vaso
26.5% vs. 35.7% p=0.05

VASST Trial. NEJM 2008;358

Norepinephrine *vs.* Vasopressin


Research

JAMA | Original Investigation

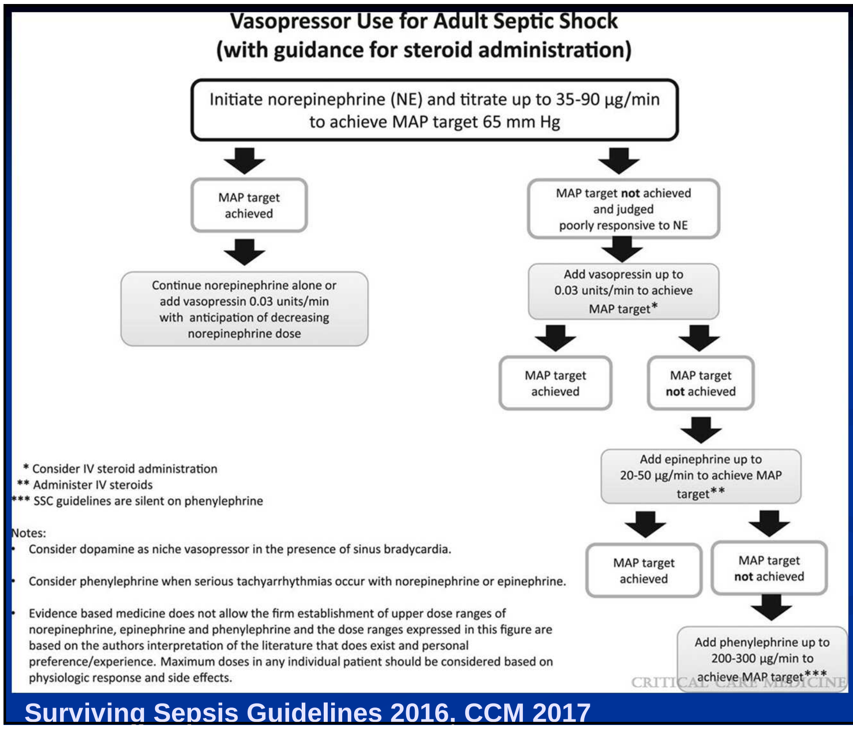
Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock

The VANISH Randomized Clinical Trial

Anthony C. Gordon, MD; Alexina J. Mason, PhD; Neeraja Thirunavukkarasu, MSc; Gavin D. Perkins, MD; Maurizio Cecconi, MD; Magda Cepkova, MD; David G. Pogson, MB BCh; Hollmann D. Aya, MD; Aisha Anjum, BSc; Gregory J. Frazier, MSc; Shalini Santhakumaran, MSc; Deborah Ashby, PhD; Stephen J. Brett, MD; for the VANISH Investigators

- About 400 septic shock subjects
  - Vaso/steroids vs. vaso vs. NE/steroids vs. NE
- No difference in kidney failure free days at 28d
- No clear renal protective effect demonstrated

JAMA. 2016;316(5):509-518. doi:10.1001/jama.2016.10485



Vasopressor Use for Adult Septic Shock (with guidance for steroid administration)

Initiate norepinephrine (NE) and titrate up to 35-90 μg/min to achieve MAP target 65 mm Hg

MAP target achieved

Continue norepinephrine alone or add vasopressin 0.03 units/min with anticipation of decreasing norepinephrine dose

MAP target **not** achieved and judged poorly responsive to NE

Add vasopressin up to 0.03 units/min to achieve MAP target*

MAP target achieved

MAP target **not achieved**

Add epinephrine up to 20-50 μg/min to achieve MAP target**

MAP target achieved

MAP target **not achieved**

Add phenylephrine up to 200-300 μg/min to achieve MAP target***

* Consider IV steroid administration
** Administer IV steroids
*** SSC guidelines are silent on phenylephrine

Notes:

- Consider dopamine as niche vasopressor in the presence of sinus bradycardia.
- Consider phenylephrine when serious tachyarrhythmias occur with norepinephrine or epinephrine.
- Evidence based medicine does not allow the firm establishment of upper dose ranges of norepinephrine, epinephrine and phenylephrine and the dose ranges expressed in this figure are based on the authors interpretation of the literature that does exist and personal preference/experience. Maximum doses in any individual patient should be considered based on physiologic response and side effects.

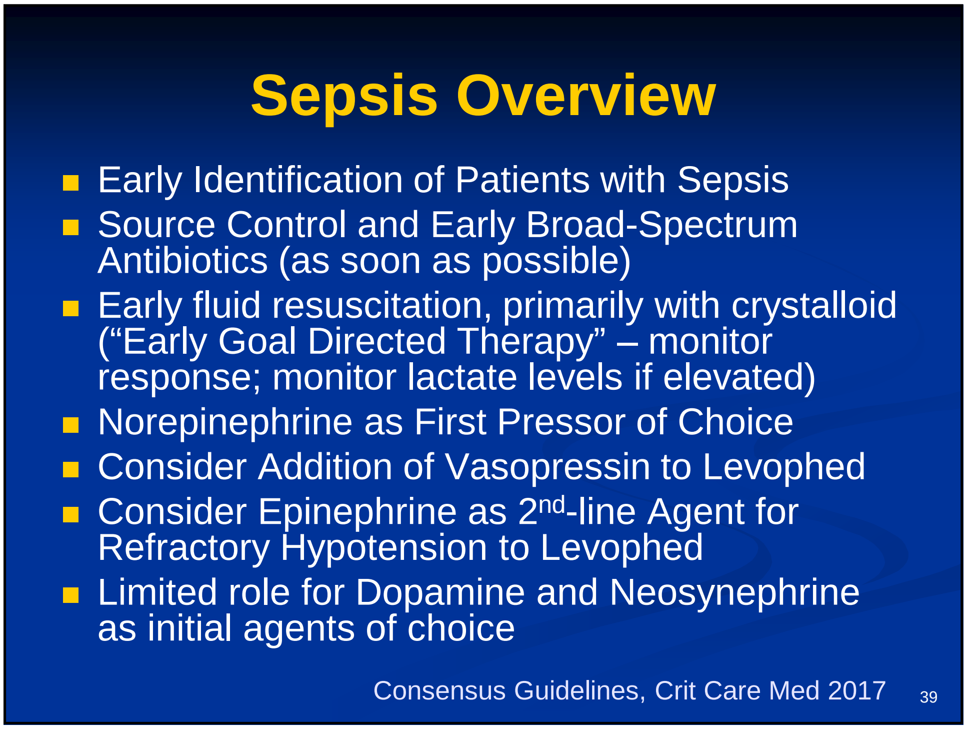
CRITICAL CARE MEDICINE

Surviving Sepsis Guidelines 2016, CCM 2017

Adjunctive Sepsis Care

- Relative Adrenal Insufficiency[1]
  - “Old protocol”: Treat if random cortisol<15 or increase of <10 with ACTH-stim?
  - “New approach”: Perhaps consider low-dose steroids only for sickest patients not responsive to vasopressors?
- Tight Glucose Control[2]
  - Target glucose adjusted to ≤180 mg/dl.
- Low Tidal Volume Ventilation in ARDS[3]
- Judicious Fluid Management in Acute Lung Injury[4]
- Protocolized Central Line Insertion and Care[5,6]

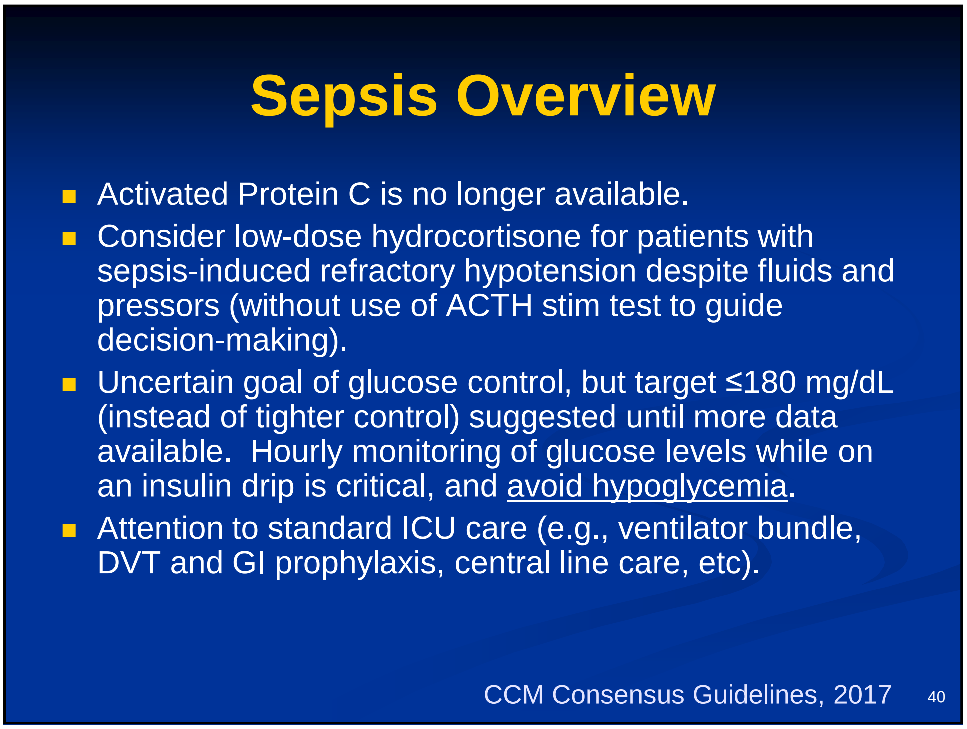
[1]NEJM 2008;358:111; [2]NEJM 2009;360:1283; [3]NEJM 2000;342:1301; [4]NEJM 2006;354:2564; [5]NEJM 2006;355:2725; [6]JAMA 2009;301:1231



Sepsis Overview

- Early Identification of Patients with Sepsis
- Source Control and Early Broad-Spectrum Antibiotics (as soon as possible)
- Early fluid resuscitation, primarily with crystalloid (“Early Goal Directed Therapy” – monitor response; monitor lactate levels if elevated)
- Norepinephrine as First Pressor of Choice
- Consider Addition of Vasopressin to Levophed
- Consider Epinephrine as 2nd-line Agent for Refractory Hypotension to Levophed
- Limited role for Dopamine and Neosynephrine as initial agents of choice

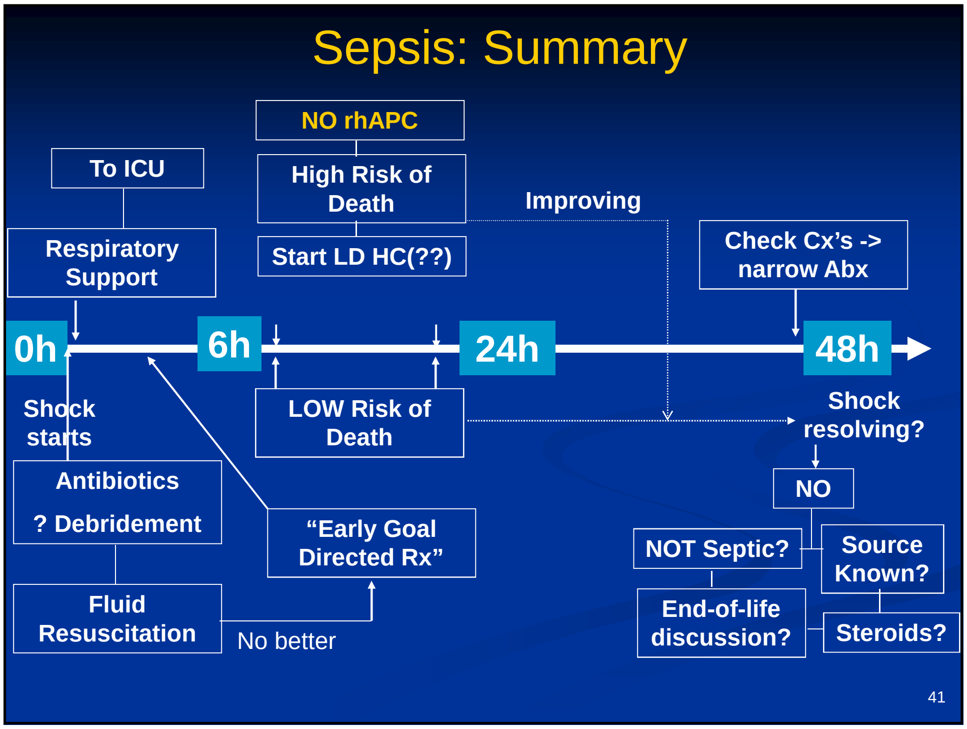
Consensus Guidelines, Crit Care Med 2017



Sepsis Overview

- Activated Protein C is no longer available.
- Consider low-dose hydrocortisone for patients with sepsis-induced refractory hypotension despite fluids and pressors (without use of ACTH stim test to guide decision-making).
- Uncertain goal of glucose control, but target ≤180 mg/dL (instead of tighter control) suggested until more data available. Hourly monitoring of glucose levels while on an insulin drip is critical, and avoid hypoglycemia.
- Attention to standard ICU care (e.g., ventilator bundle, DVT and GI prophylaxis, central line care, etc).

CCM Consensus Guidelines, 2017



Sepsis: Summary

NO rhAPC

To ICU

High Risk of Death

Improving

Respiratory Support

Start LD HC(??)

Check Cx's -> narrow Abx

0h

6h

24h

48h

Shock starts

LOW Risk of Death

Shock resolving?

Antibiotics

? Debridement

"Early Goal Directed Rx"

NO

NOT Septic?

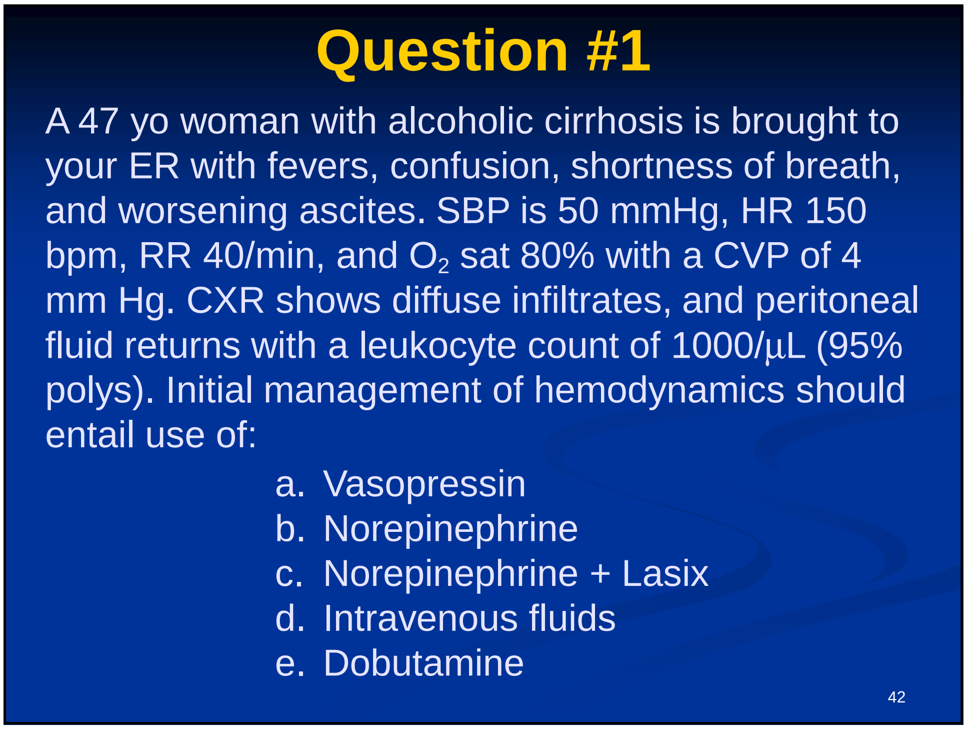
Source Known?

Fluid Resuscitation

No better

End-of-life discussion?

Steroids?



Question #1

A 47 yo woman with alcoholic cirrhosis is brought to your ER with fevers, confusion, shortness of breath, and worsening ascites. SBP is 50 mmHg, HR 150 bpm, RR 40/min, and O_2 sat 80% with a CVP of 4 mm Hg. CXR shows diffuse infiltrates, and peritoneal fluid returns with a leukocyte count of 1000/µL (95% polys). Initial management of hemodynamics should entail use of:

a. Vasopressin
b. Norepinephrine
c. Norepinephrine + Lasix
d. Intravenous fluids
e. Dobutamine

Question #1

A 47 yo woman with alcoholic cirrhosis is brought to your ER with fevers, confusion, shortness of breath, and worsening ascites. SBP is 50 mmHg, HR 150 bpm, RR 40/min, and O_2 sat 80% with a CVP of 4 mm Hg. CXR shows diffuse infiltrates, and peritoneal fluid returns with a leukocyte count of 1000/µL (95% polys). Initial management of hemodynamics should entail use of:

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c. Norepinephrine + Lasix
d. Intravenous fluids
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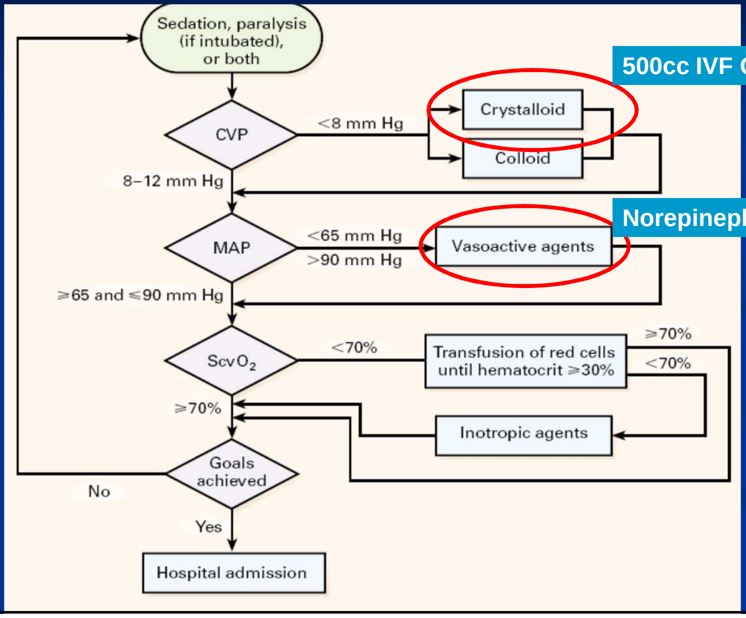
"EARLY Goal-Directed Therapy"

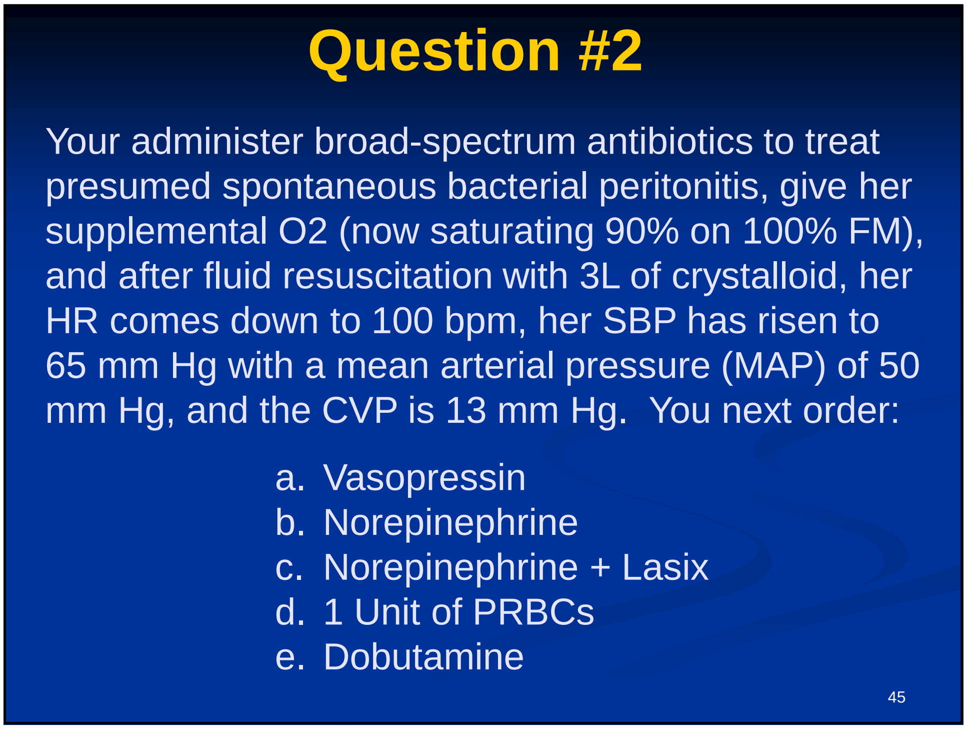
INTERVENTION


Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
$ScvO_2$
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

500cc IVF Q 30 min!

Norepinephrine

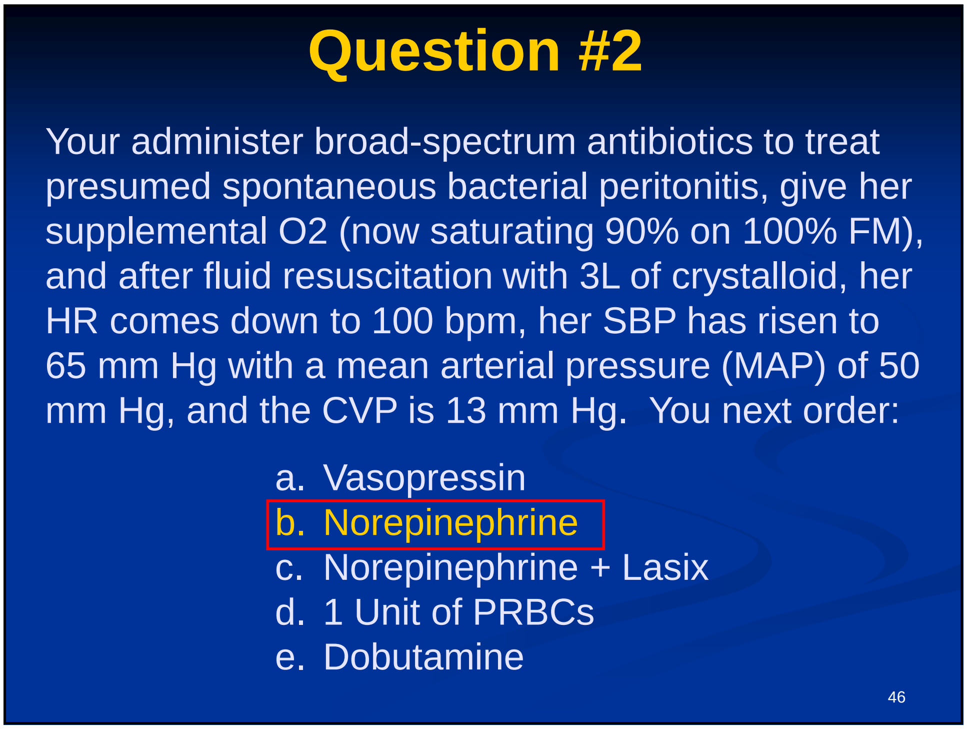
NEJM 2001; 345:1368 (© 2001 Mass Medical Society. All Rights Reserved). Adapted w/Permission.



Question #2

Your administer broad-spectrum antibiotics to treat presumed spontaneous bacterial peritonitis, give her supplemental O2 (now saturating 90% on 100% FM), and after fluid resuscitation with 3L of crystalloid, her HR comes down to 100 bpm, her SBP has risen to 65 mm Hg with a mean arterial pressure (MAP) of 50 mm Hg, and the CVP is 13 mm Hg. You next order:

a. Vasopressin
b. Norepinephrine
c. Norepinephrine + Lasix
d. 1 Unit of PRBCs
e. Dobutamine



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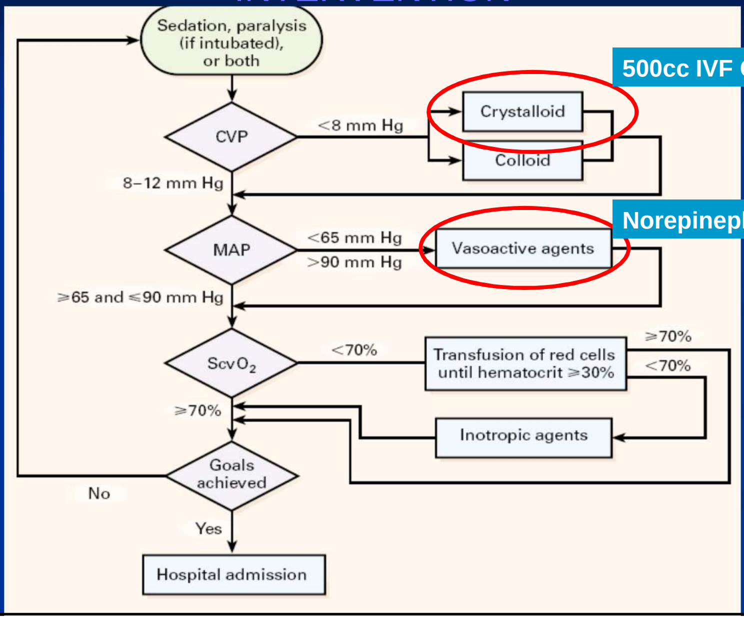
a. Vasopressin
b. Norepinephrine
c. Norepinephrine + Lasix
d. 1 Unit of PRBCs
e. Dobutamine

“*EARLY* Goal-Directed Therapy”

INTERVENTION


Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO$_2$
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

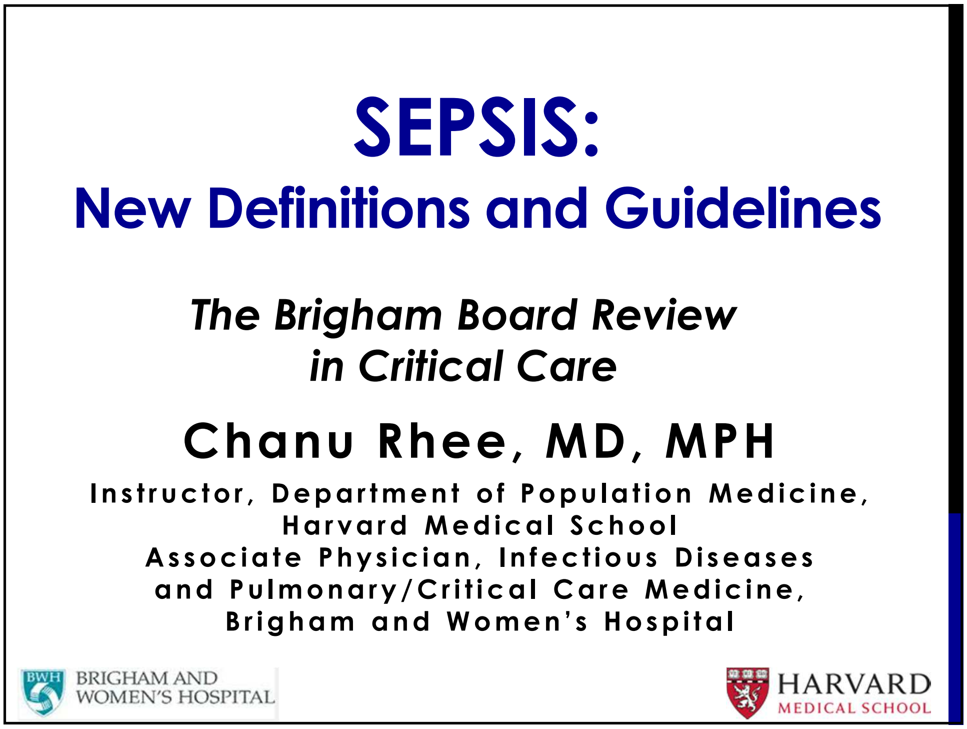
500cc IVF Q 30 min!

Norepinephrine

NEJM 2001; 345:1368 (© 2001 Mass Medical Society. All Rights Reserved). Adapted w/Permission.

A Few Key References

- C.I. Pro, D.M. Yealy, J.A. Kellum, D.T. et al. A randomized trial of protocol-based care for early septic shock, N. Engl. J. Med. 370(18) (2014) 1683-93.
- M. Singer, C.S. Deutschman, C.W. Seymour, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), JAMA 315(8) (2016) 801-10.
- A. Rhodes, L.E. Evans, W. Alhazzani, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016, Crit. Care Med. 45(3) (2017) 486-552.



SEPSIS:

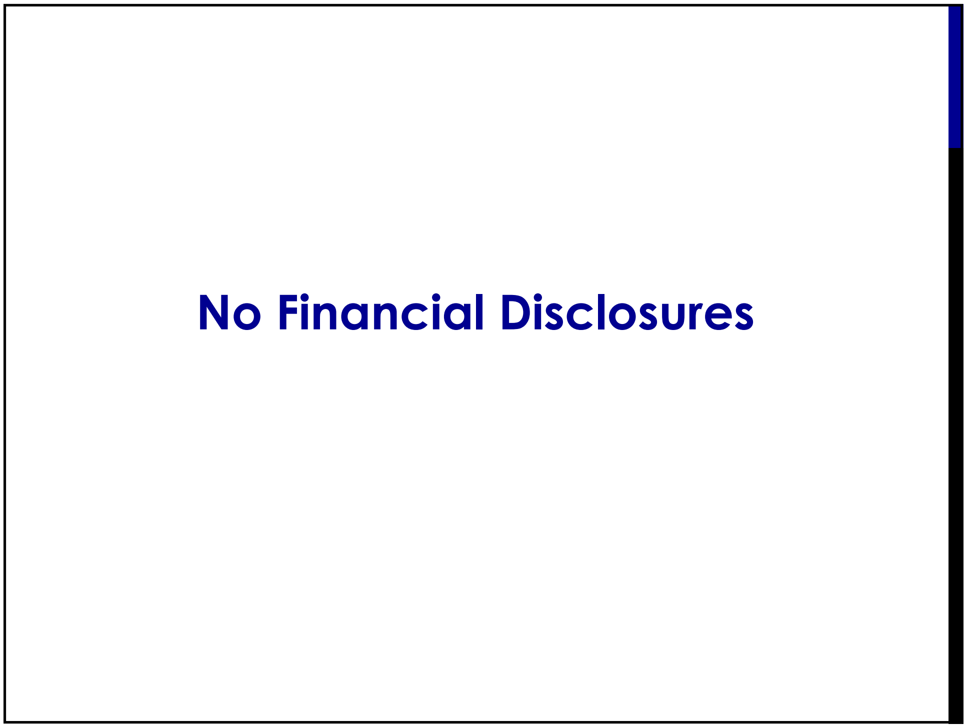
New Definitions and Guidelines

The Brigham Board Review
in Critical Care

Chanu Rhee, MD, MPH
Instructor, Department of Population Medicine,
Harvard Medical School
Associate Physician, Infectious Diseases
and Pulmonary/Critical Care Medicine,
Brigham and Women's Hospital

BRIGHAM AND
WOMEN'S HOSPITAL

HARVARD
MEDICAL SCHOOL



No Financial Disclosures

Outline

1. Epidemiology and Burden
2. Definitions and Diagnosis
3. Updates to Management Guidelines

Sepsis: See it, Treat it, Defeat it

The Brigham Health Sepsis Task Force

Surviving Sepsis Campaign

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

SEPSIS ALLIANCE®
Suspect Sepsis. Save Lives.™
I'VE BEEN DIAGNOSED WITH SEPSIS
SOMEONE I KNOW WAS DIAGNOSED
LIFE AFTER SEPSIS
SHARE YOUR STORY

Why All the Fuss About Sepsis?

The New York Times

Friday, September 19, 2014 | Today's Paper | Video | Weather

World U.S. Politics New York Business Opinion Technology Science Health Sports Arts Style Dining Home Travel Magazine Real Estate ALL

N.Y. / REGION

An Effort to Raise Awareness of Sepsis, Led by Families Touched by It

About New York

One evening in late spring, Ken Fitzgerald, a US Airways pilot, was on a layover in a hotel near Kennedy International Airport when people he had been in touch with by email and phone, but whom he had never met, called him. Would he like to join them for a burger?

SEPTEMBER SEPSIS SAY SEPSIS SAVE LIVES
SEPSISAWARENESSMONTH.ORG

CDC to Launch New Sepsis Initiative

Posted on April 26, 2016

Patty Duke and Sepsis

Passing of an Icon Spurs a National Conversation

READ MORE

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

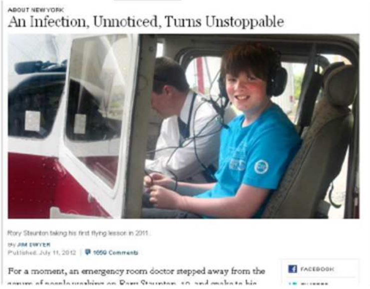
Sepsis Burden in the U.S.

- **>1 million sepsis cases/year[1]**
- **#1 cause of death in noncoronary ICU's[2]**
- **Most expensive condition treated in hospitals[3]**
- **May contribute to up to 30-50% of hospital deaths[4]**
- **Survivors also at high risk for recurrent sepsis, readmission, cognitive and functional impairment[5]**

1. Gaieski, Crit Care Med (2011)
2. Minino, NCHS Data Brief (2012)
3. Torio, HCUP Statistical Brief #160 (2013)
4. Liu, JAMA (2014)
5. Winters, Crit Care Med (2010)

Recent Public Attention

[redacted] The New York Times [redacted]



ABOUT NEW YORK

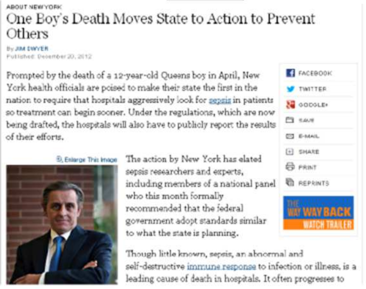
An Infection, Unnoticed, Turns Unstoppable

Rory Staunton taking his first flying lesson in 2011.

By JIM DWYER

Published: July 11, 2012 | 1050 Comments

For a moment, an emergency room doctor stepped away from the



ABOUT NEW YORK

One Boy's Death Moves State to Action to Prevent Others

By JIM DWYER

Published: December 20, 2012

Prompted by the death of a 12-year-old Queens boy in April, New York health officials are poised to make their state the first in the nation to require that hospitals aggressively look for sepsis in patients so treatment can begin sooner. Under the regulations, which are now being drafted, the hospitals will also have to publicly report the results of their efforts.

The action by New York has elated sepsis researchers and experts, including members of a national panel who this month formally recommended that the federal government adopt standards similar to what the state is planning.

Though little known, sepsis, an abnormal and self-destructive immune response to infection or illness, is a leading cause of death in hospitals. It often progresses to

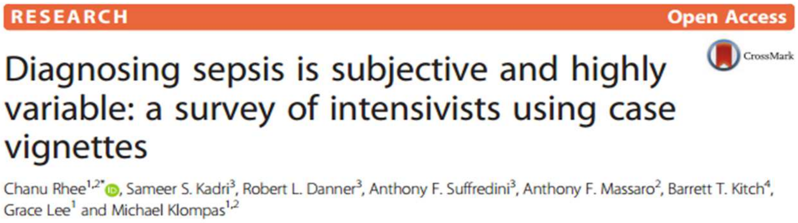
- **April 2012 – 12 year old boy died of septic shock in NY City**
  - Symptoms not initially recognized by pediatrician / ER
- **Family embarked on nationwide campaign to raise sepsis awareness and prevent further deaths**
  - Established the Rory Staunton Foundation

A New Era of Policy Initiatives for Sepsis

- **In 2012, New York State mandated sepsis protocols in all state hospitals ("Rory's Regulations")**
  - Followed by public reporting and benchmarking for protocol adherence
- **CMS sepsis quality measure (SEP-1) took effect October 1st, 2015**
  - Pay-for-reporting measure: hospitals report compliance with 3 and 6 hour bundles for patients diagnosed with sepsis

So what *is* sepsis, really?

- **Sepsis was described more than 2,000 years ago**
- **Clearly refers to a "bad infection"**
- **But clinicians still struggle to define it**
- **Florid cases (e.g., meningococcemia) are a minority of cases**



RESEARCH **Open Access**

Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes

Chanu Rhee[1,2*], Sameer S. Kadri[3], Robert L. Danner[3], Anthony F. Suffredini[3], Anthony F. Massaro[2], Barrett T. Kitch[4], Grace Lee[1] and Michael Klompas[1,2]

- **5 case vignettes of patients with suspected or confirmed infection and possible organ dysfunction distributed to 94 academic intensivists**
  - Respondents classified cases as SIRS alone, sepsis, severe sepsis, septic shock, or none of the above

Rhee et al, Crit Care 2016

Case Vignette

67 year old male with severe congestive heart failure presents with several days of progressive shortness of breath, lower extremity swelling, malaise, productive cough, and subjective fevers.

Low grade fever in ED, rapid atrial fibrillation, hypotensive, with signs of volume overload

Labs with elevated WBC, lactate, and acute kidney injury

Chest X-ray with pulmonary edema and possible left lower lobe infiltrate

Case Vignette, continued

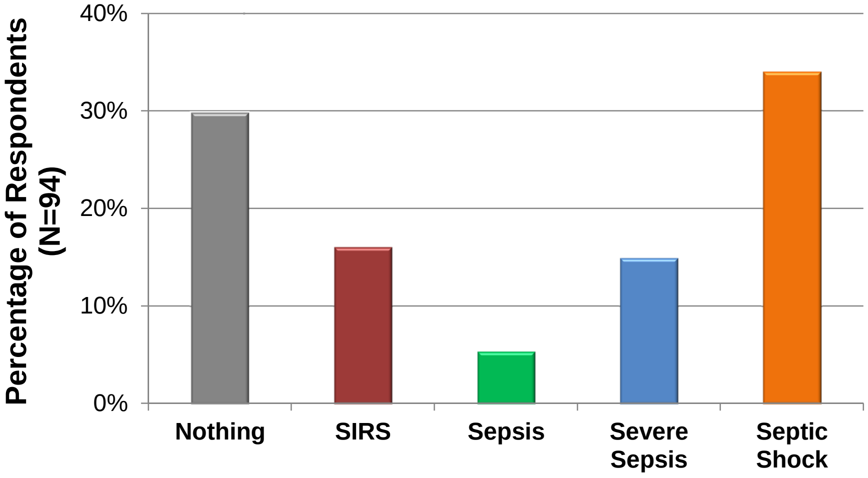
Gets fluids, diltiazem, and antibiotics

Decompensates into respiratory failure, shock and altered mental status, requiring intubation and vasopressors

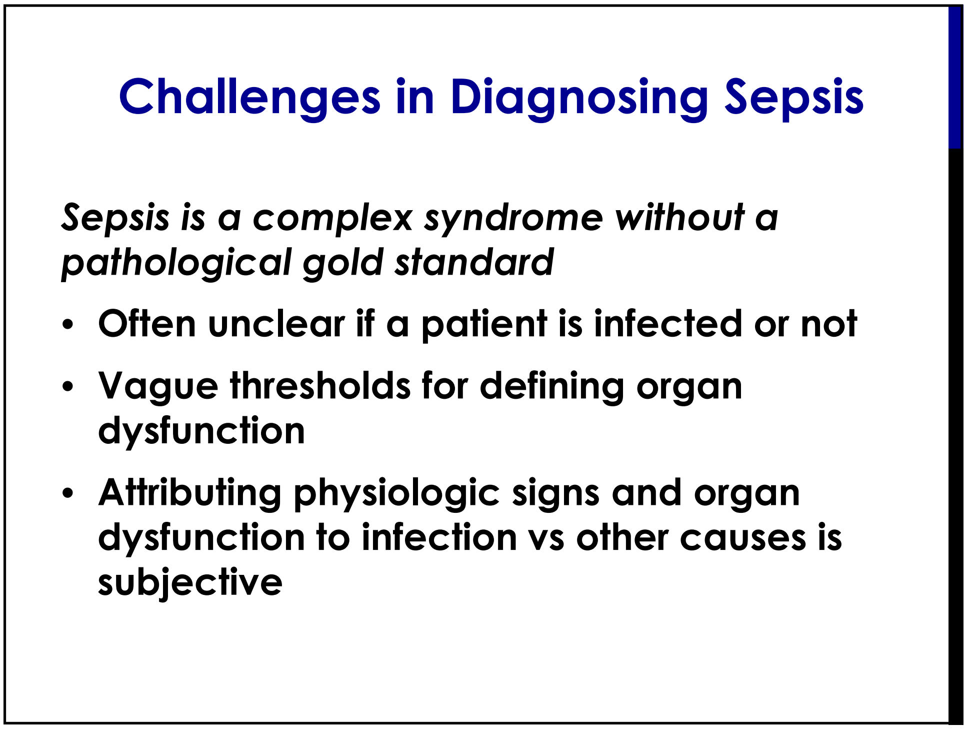
Admitted to ICU – continued on vasopressors, antibiotics, anti-arrhythmic medications, and diuresis

Improves and gets extubated. Blood and sputum cultures negative. Finishes course of antibiotics and discharged.

Is this Sepsis?



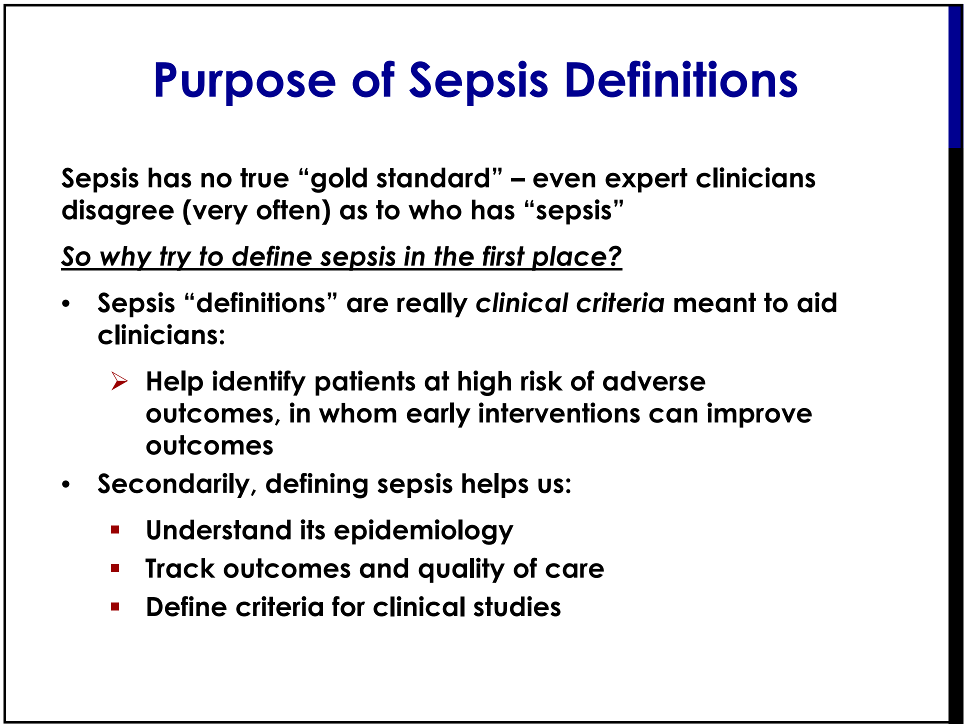
Rhee et al, Crit Care 2016



Challenges in Diagnosing Sepsis

Sepsis is a complex syndrome without a pathological gold standard

- Often unclear if a patient is infected or not
- Vague thresholds for defining organ dysfunction
- Attributing physiologic signs and organ dysfunction to infection vs other causes is subjective

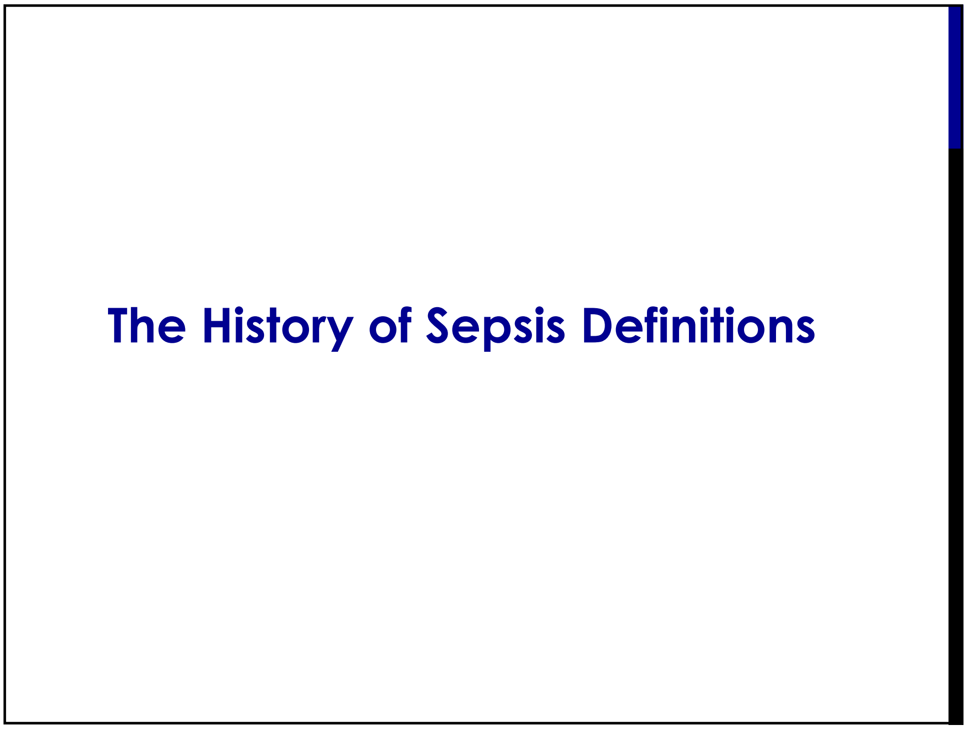


Purpose of Sepsis Definitions

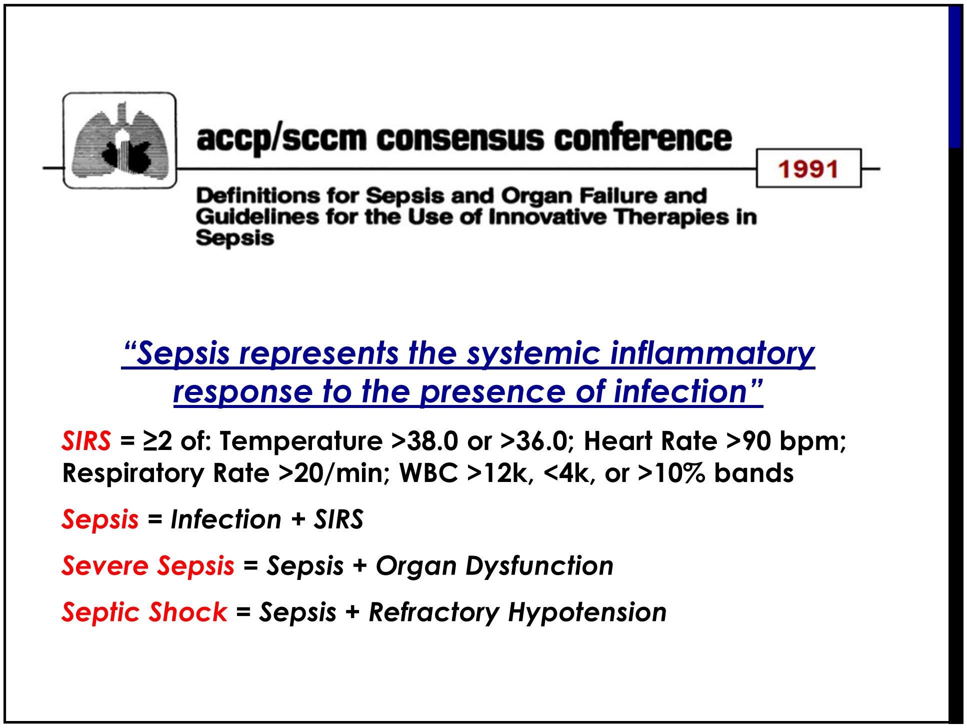
Sepsis has no true "gold standard" – even expert clinicians disagree (very often) as to who has "sepsis"

So why try to define sepsis in the first place?

- Sepsis "definitions" are really *clinical criteria* meant to aid clinicians:
  - ➢ Help identify patients at high risk of adverse outcomes, in whom early interventions can improve outcomes
- Secondarily, defining sepsis helps us:
  - ▪ Understand its epidemiology
  - ▪ Track outcomes and quality of care
  - ▪ Define criteria for clinical studies



The History of Sepsis Definitions



accp/sccm consensus conference

1991

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

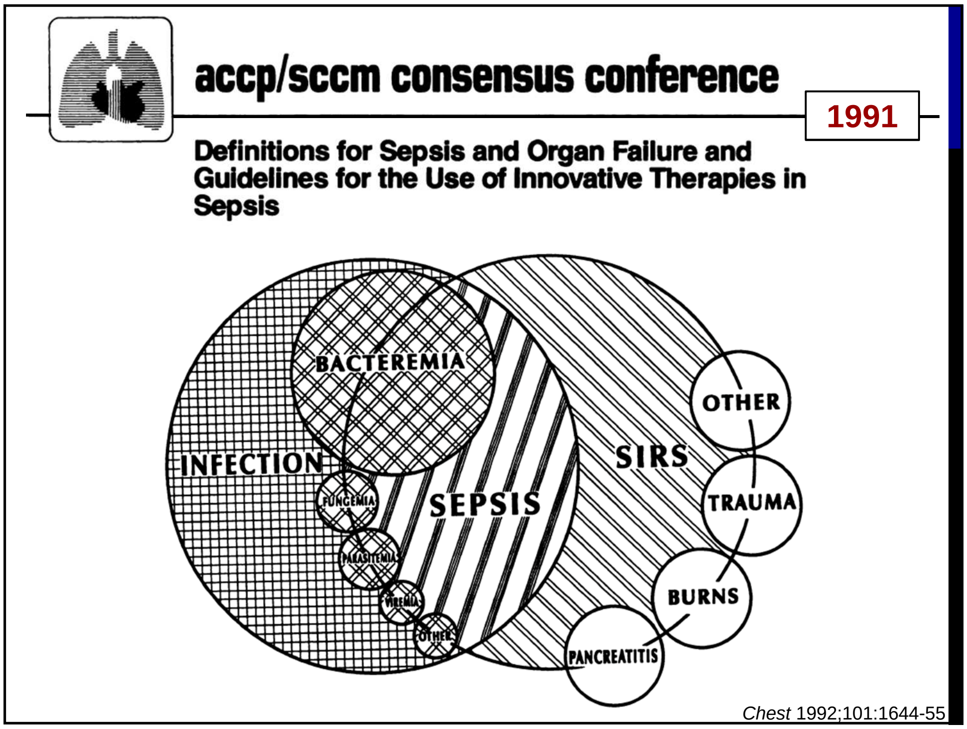
"Sepsis represents the systemic inflammatory response to the presence of infection"

SIRS = ≥2 of: Temperature >38.0 or >36.0; Heart Rate >90 bpm; Respiratory Rate >20/min; WBC >12k, <4k, or >10% bands

Sepsis = *Infection + SIRS*

Severe Sepsis = *Sepsis + Organ Dysfunction*

Septic Shock = *Sepsis + Refractory Hypotension*

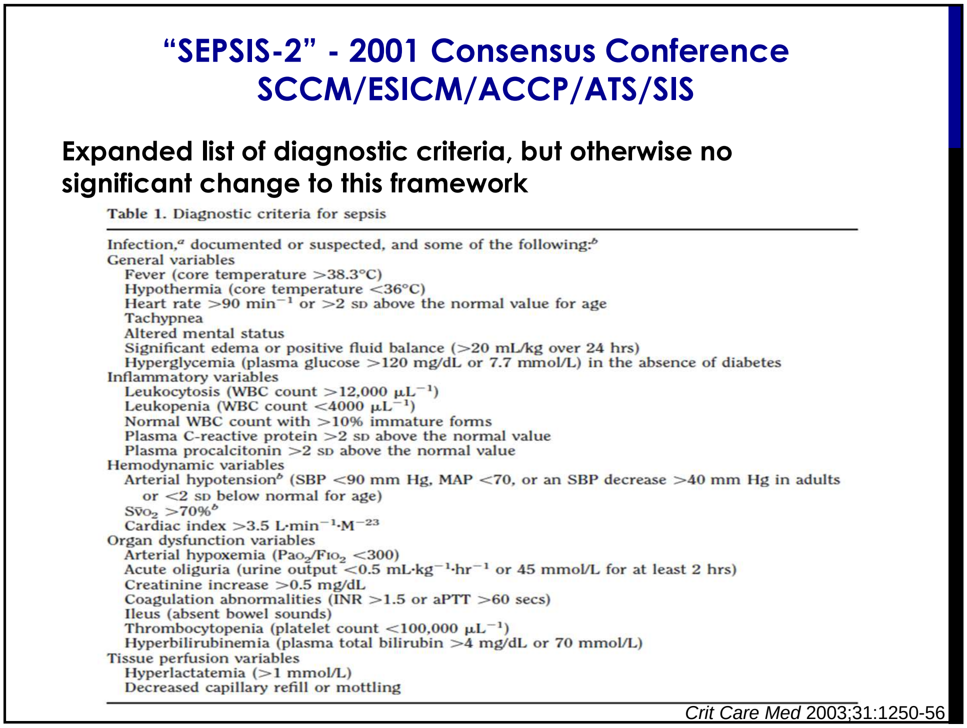


accp/sccm consensus conference

1991

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

Chest 1992;101:1644-55



"SEPSIS-2" - 2001 Consensus Conference SCCM/ESICM/ACCP/ATS/SIS

Expanded list of diagnostic criteria, but otherwise no significant change to this framework

Table 1. Diagnostic criteria for sepsis

Infection,^{a} documented or suspected, and some of the following:^{b}
- General variables
  - Fever (core temperature >38.3°C)
  - Hypothermia (core temperature <36°C)
  - Heart rate >90 min^{-1} or >2 SD above the normal value for age
  - Tachypnea
  - Altered mental status
  - Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
  - Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes
- Inflammatory variables
  - Leukocytosis (WBC count >12,000 μL^{-1})
  - Leukopenia (WBC count <4000 μL^{-1})
  - Normal WBC count with >10% immature forms
  - Plasma C-reactive protein >2 SD above the normal value
  - Plasma procalcitonin >2 SD above the normal value
- Hemodynamic variables
  - Arterial hypotension^b (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
  - $S\bar{v}O_2$ >70%^{b}
  - Cardiac index >3.5 $L \cdot min^{-1} \cdot M^{-23}$
- Organ dysfunction variables
  - Arterial hypoxemia (Pa_{O_2}/F_{IO_2} <300)
  - Acute oliguria (urine output <0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$ or 45 mmol/L for at least 2 hrs)
  - Creatinine increase >0.5 mg/dL
  - Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
  - Ileus (absent bowel sounds)
  - Thrombocytopenia (platelet count <100,000 μL^{-1})
  - Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
- Tissue perfusion variables
  - Hyperlactatemia (>1 mmol/L)
  - Decreased capillary refill or mottling

Crit Care Med 2003;31:1250-56

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

Offered some operational criteria and cutoffs for organ dysfunction (for the first time)

→ **Adapted into the current CMS definition of severe sepsis**

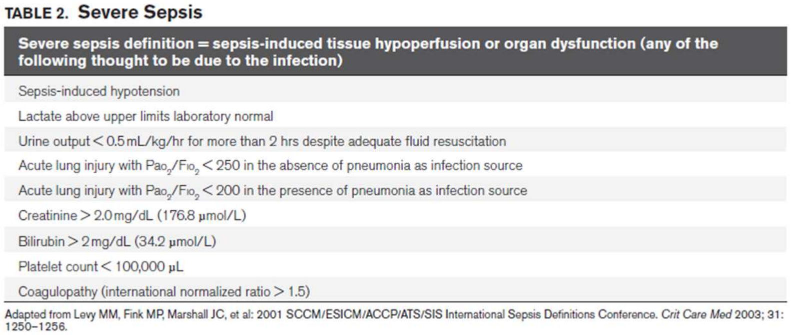


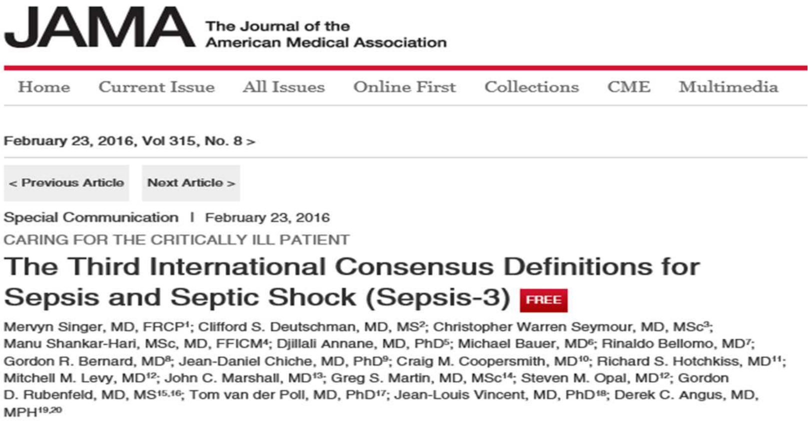
TABLE 2. **Severe Sepsis**

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with $\text{Pao}_2/\text{Fio}_2$ < 250 in the absence of pneumonia as infection source
Acute lung injury with $\text{Pao}_2/\text{Fio}_2$ < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 µmol/L)
Bilirubin > 2 mg/dL (34.2 µmol/L)
Platelet count < 100,000 µL
Coagulopathy (international normalized ratio > 1.5)

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

No guidelines on how to interpret pre-existing organ dysfunction

The New "Sepsis-3" Definitions



February 23, 2016, Vol 315, No. 8 >

Special Communication | February 23, 2016

CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

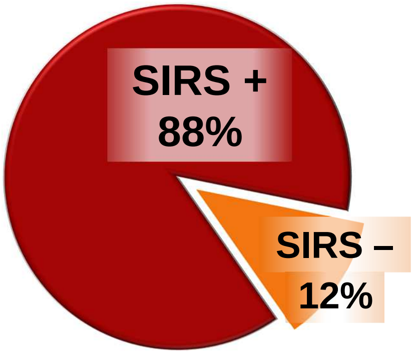
Mervyn Singer, MD, FRCP[1]; Clifford S. Deutschman, MD, MS[2]; Christopher Warren Seymour, MD, MSc[3]; Manu Shankar-Hari, MSc, MD, FFICM[4]; Djillali Annane, MD, PhD[5]; Michael Bauer, MD[6]; Rinaldo Bellomo, MD[7]; Gordon R. Bernard, MD[8]; Jean-Daniel Chiche, MD, PhD[9]; Craig M. Coopersmith, MD[10]; Richard S. Hotchkiss, MD[11]; Mitchell M. Levy, MD[12]; John C. Marshall, MD[13]; Greg S. Martin, MD, MSc[14]; Steven M. Opal, MD[12]; Gordon D. Rubenfeld, MD, MS[15,16]; Tom van der Poll, MD, PhD[17]; Jean-Louis Vincent, MD, PhD[18]; Derek C. Angus, MD, MPH[19,20]

Why a New Definition?

- **SIRS criteria are problematic:**
  - **Nonspecific for infection/sepsis**
  - Can also **miss cases of infection + organ dysfunction**
  - Sepsis thought to be a ***dysregulated inflammatory response*** to infection, but SIRS is actually physiologic
    - **Organ dysfunction** is what crosses the line
- **"Severe sepsis" is confusing -** many clinicians use "sepsis" and "severe sepsis" interchangeably
- **Poorly defined thresholds for organ dysfunction and for septic shock →** heterogeneity in study cohorts
- **Septic shock felt to be more than just sepsis with hypotension/cardiovascular dysfunction**

Severe Sepsis and SIRS

109,663 patients with infection and organ dysfunction admitted to 172 ICUs in Australia and New Zealand, 2000-2013



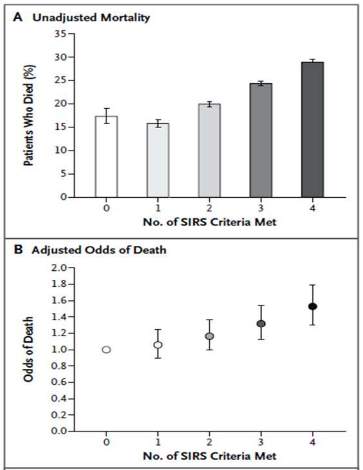
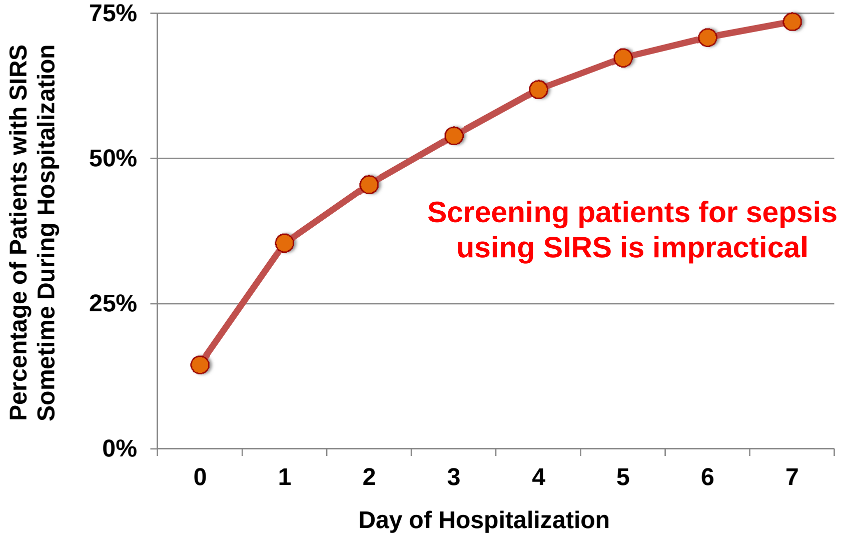


Figure 2. Mortality among Patients with Severe Sepsis, According to Number of SIRS Criteria Met.

Kaukonen et al, NEJM 2015;372:1629-38

Incidence of SIRS in Ward Patients

Retrospective analysis of 269,951 patients in 5 Chicago hospitals, 2008-2013

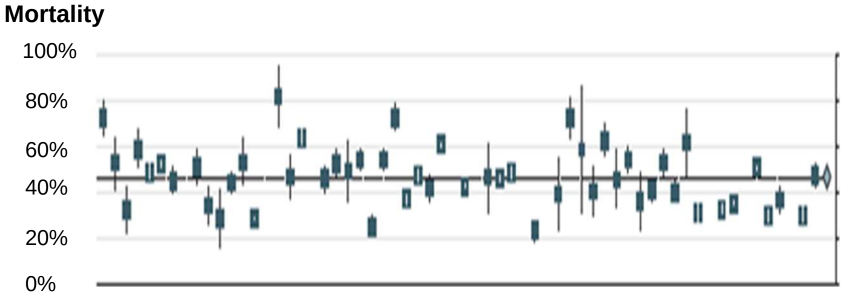


Screening patients for sepsis using SIRS is impractical

Churpek et al, Am J Resp Crit Care Med 2015;192:958-64

Heterogeneity in Septic Shock Mortality

Metanalysis of 44 studies



Mortality ranges from 20-80%!!

Shankar-Hari et al, JAMA 2016; 315:775-87

Major Conceptual Changes in Sepsis-3

"Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection"

"Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone"

SIRS criteria removed from definition

"Severe Sepsis" removed from definition

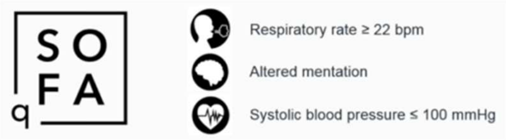
→ "Sepsis" (Infection + Organ Dysfunction)

"Septic shock" requires refractory hypotension AND elevated lactate

Introduced concept of "quick SOFA"

Sepsis-3: Operational Criteria

- **Sepsis = Infection + ↑SOFA score by ≥2 points from baseline**
  - Baseline SOFA score should be assumed to be 0, unless known pre-existing organ dysfunction
- **In out-of-hospital, ED, or general ward settings:**
  - Suspected infection + **≥2 "Quick SOFA"** criteria should be used to identify patients with likely sepsis and high risk of poor outcome:



Respiratory rate ≥ 22 bpm
Altered mentation
Systolic blood pressure ≤ 100 mmHg

- **Septic Shock = Infection + Vasopressor-Dependent Hypotension + Lactate >2.0 mmol/L in absence of hypovolemia**

SOFA Score: 6 Organ Systems, 0-4 Points

Points	0	1	2	3	4
PaO2/FiO2	≥400	<400	<300	<200 + mechanical ventilation	<100 + mechanical ventilation
Platelets	≥150	<150	<100	<50	<20
Bilirubin	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Blood Pressure	MAP ≥70	MAP <70	Dopamine <5 or Dobutamine	Dopamine 5.1-15 or Epinephrine <0.1 or Norepinephrine <0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Creatinine	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500cc urine/d	>5.0 or <200cc urine/d

Vincent et al, Intensive Care Med 1996

Where did this come from?

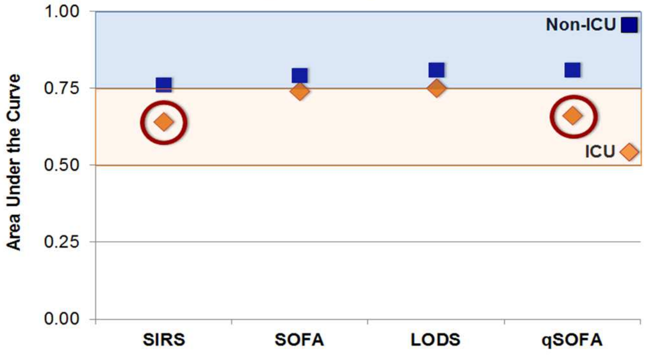
- **Large EHR datasets used to develop their criteria (vs prior definitions based only on expert opinion)**
  - 1.3 million EHR encounters from 2010-2012 at 12 hospitals in University of Pittsburgh Medical System
  - ~150,000 patients identified with **"suspected infection"**
    - Any clinical culture + Non-prophylactic antibiotic
- **Compared various criteria for ability to predict in-hospital mortality, ICU stay ≥ 3 days, or both**
- ***Rationale: No gold standard for sepsis – but** bad **outcomes (prolonged ICU stay and/or death) are more likely amongst patients with sepsis than uncomplicated infection***

Sepsis-3 Derivation of Quick SOFA

- 21 bedside and laboratory criteria from Sepsis-2
- Multivariate analysis identified parsimonious criteria with good predictive ability for death / prolonged ICU stay:
  - ✓ **SBP <=100**
  - ✓ **RR >=22**
  - ✓ **GCS of ≤13**

  } 2/3 criteria
- Performance same when GCS recoded as <15 (i.e., any AMS)
- Robust to sensitivity analyses varying time window
- **Addition of lactate at different cutoffs did not significantly improve predictive validity**

SIRS vs SOFA vs LODS vs qSOFA for predicting hospital mortality



- **qSOFA ≈ full SOFA score outside the ICU and superior to SIRS**
- **Within the ICU, SOFA score and LODS > qSOFA and SIRS**
- **Similar results in validation in 4 external datasets**

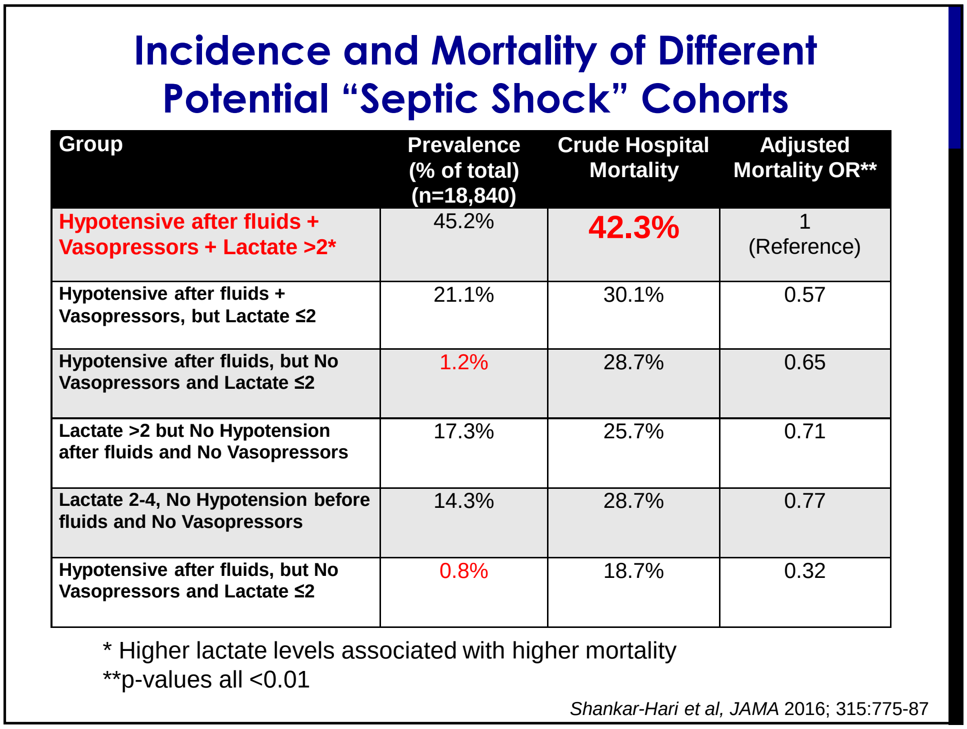
Seymour et al, JAMA 2016;315:762-774

Summary of Sepsis-3 Derivation

- **qSOFA – simple and easy to apply at the bedside**
  - In patients with suspected infection, identifies subset at high risk of poor outcomes
- **SIRS has relatively poor predictive / discriminatory power**
- **SOFA score and LODS performed similarly; superior to qSOFA or SIRS in the ICU**
  - → ***SOFA chosen for definition operationalization due to greater simplicity and familiarity***

Septic Shock Derivation: Methods

- 3 variables identified via Delphi Method to test in cohort studies:
  1. **Hypotension (MAP <65 mmHg)**
  2. **Vasopressor requirement**
  3. **Elevated Lactate**
- Descriptive analyses performed in the Surviving Sepsis Campaign database to examine various combinations
- Validated in the University of Pittsburgh Medical Center and Kaiser Permanente Northern California data sets

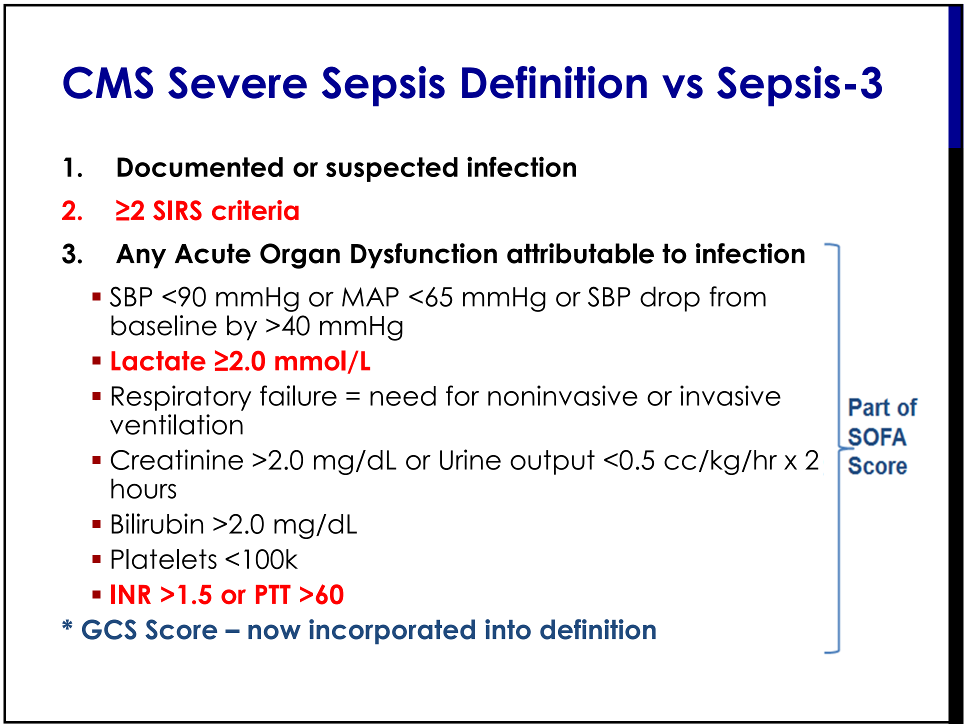


Incidence and Mortality of Different Potential "Septic Shock" Cohorts

Group	Prevalence (% of total) (n=18,840)	Crude Hospital Mortality	Adjusted Mortality OR**
Hypotensive after fluids + Vasopressors + Lactate >2*	45.2%	**42.3%**	1 (Reference)
Hypotensive after fluids + Vasopressors, but Lactate ≤2	21.1%	30.1%	0.57
Hypotensive after fluids, but No Vasopressors and Lactate ≤2	1.2%	28.7%	0.65
Lactate >2 but No Hypotension after fluids and No Vasopressors	17.3%	25.7%	0.71
Lactate 2-4, No Hypotension before fluids and No Vasopressors	14.3%	28.7%	0.77
Hypotensive after fluids, but No Vasopressors and Lactate ≤2	0.8%	18.7%	0.32

* Higher lactate levels associated with higher mortality
**p-values all <0.01

Shankar-Hari et al, JAMA 2016; 315:775-87



CMS Severe Sepsis Definition vs Sepsis-3

1. **Documented or suspected infection**
2. **≥2 SIRS criteria**
3. **Any Acute Organ Dysfunction attributable to infection**
    - SBP <90 mmHg or MAP <65 mmHg or SBP drop from baseline by >40 mmHg
    - **Lactate ≥2.0 mmol/L**
    - Respiratory failure = need for noninvasive or invasive ventilation
    - Creatinine >2.0 mg/dL or Urine output <0.5 cc/kg/hr x 2 hours
    - Bilirubin >2.0 mg/dL
    - Platelets <100k
    - **INR >1.5 or PTT >60**

*** GCS Score – now incorporated into definition**

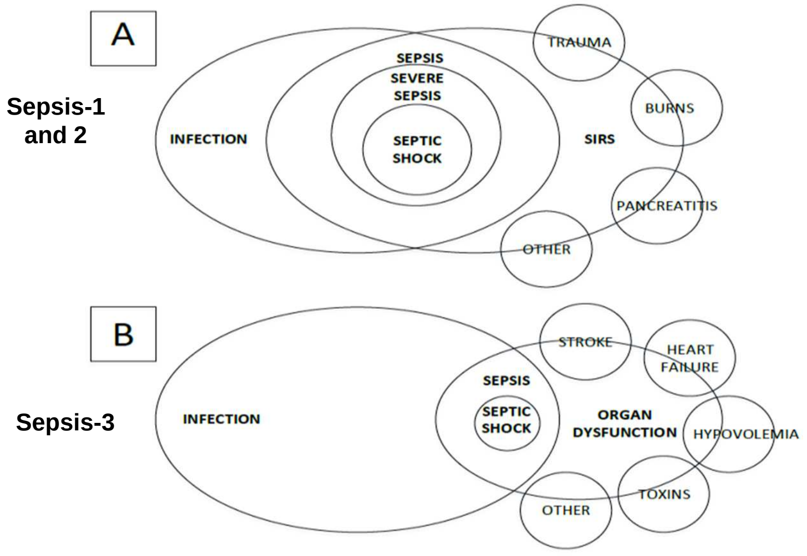
Part of SOFA Score

CMS Septic Shock vs Sepsis-3

Suspected infection +

- Persistent hypotension after fluids
- OR lactate ≥ 4.0 mmol/L
- Requiring vasopressors +
- Serum lactate level >2 mmol/L

Conceptual Changes in Sepsis-3


A
Sepsis-1 and 2
INFECTION
SEPSIS
SEVERE SEPSIS
SEPTIC SHOCK
SIRS
TRAUMA
BURNS
PANCREATITIS
OTHER
B
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SEPSIS
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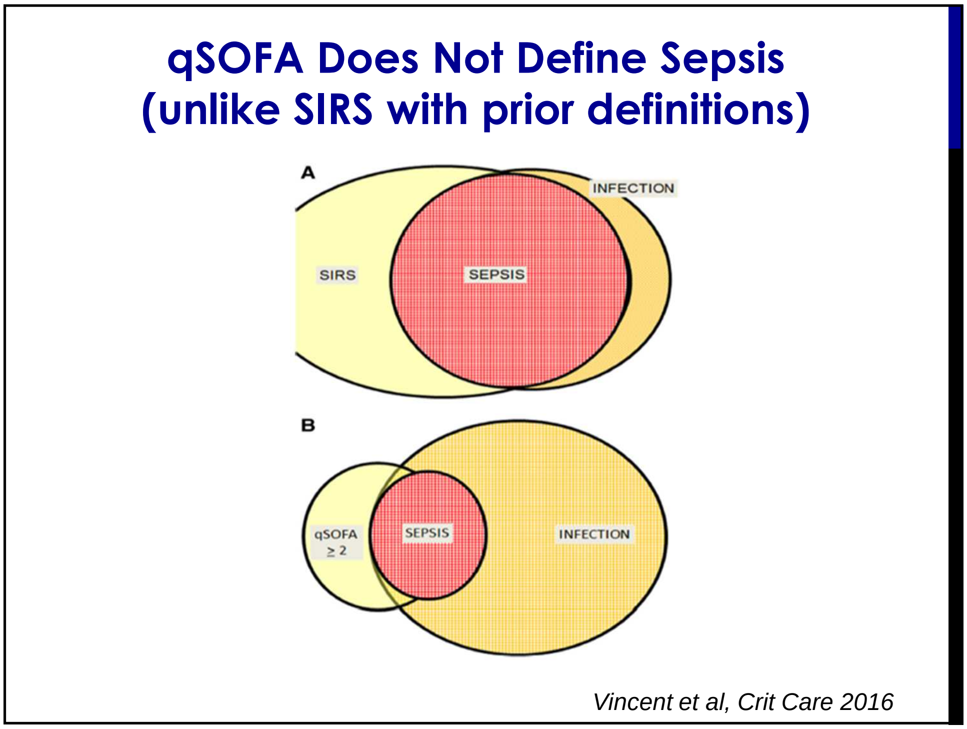
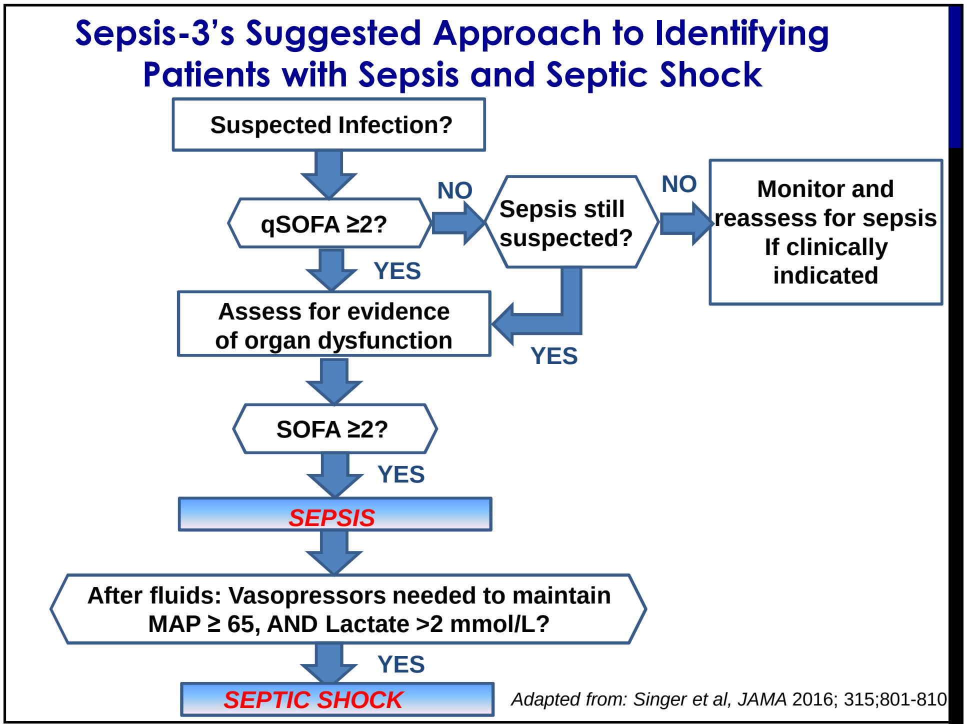
ORGAN DYSFUNCTION
STROKE
HEART FAILURE
HYPOVOLEMIA
TOXINS
OTHER



qSOFA Does Not Define Sepsis (unlike SIRS with prior definitions)

Vincent et al, Crit Care 2016



Sepsis-3's Suggested Approach to Identifying Patients with Sepsis and Septic Shock

Suspected Infection?

qSOFA ≥2?

NO

Sepsis still suspected?

NO

Monitor and reassess for sepsis If clinically indicated

YES

Assess for evidence of organ dysfunction

YES

SOFA ≥2?

YES

SEPSIS

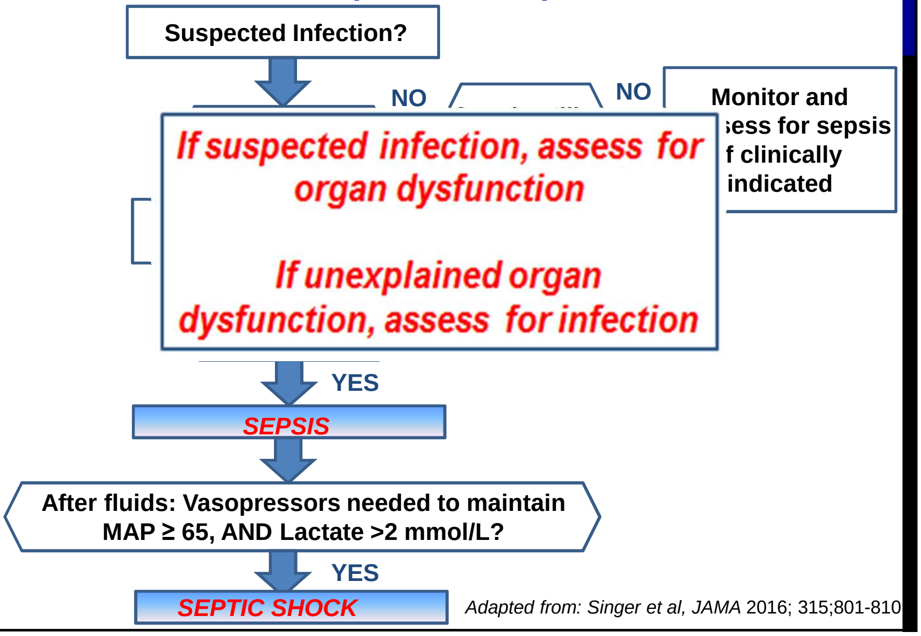
After fluids: Vasopressors needed to maintain MAP ≥ 65, AND Lactate >2 mmol/L?

YES

SEPTIC SHOCK

Adapted from: Singer et al, JAMA 2016; 315;801-810

Sepsis-3's Suggested Approach to Identifying Patients with Sepsis and Septic Shock


Suspected Infection?

NO

NO

Monitor and
ess for sepsis
f clinically
indicated

If suspected infection, assess for organ dysfunction

If unexplained organ dysfunction, assess for infection

YES

SEPSIS

After fluids: Vasopressors needed to maintain MAP ≥ 65, AND Lactate >2 mmol/L?

YES

SEPTIC SHOCK

Adapted from: Singer et al, JAMA 2016; 315;801-810

Surviving Sepsis Campaign

Surviving Sepsis Campaign Responds to Sepsis-3
March 1, 2016

SSC's approach: essentially no different than before!

Step 1: Screen for Infection

- *SIRS may be a sign of infection*

Step 2: Screen for Organ Dysfunction

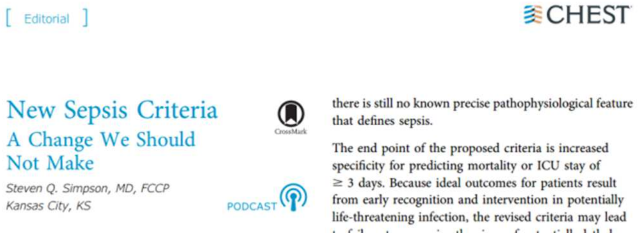
- If organ dysfunction (including lactate >2.0)→ initiate 3-hour bundle
- If 2/3 qSOFA critieria → "strongly consider closer monitoring"

Step 3: If hypotensive or lactate >=2.0 → 30 ml/kg crystalloid, with reassessesment of volume responsiveness or tissuee perfusion

New Definitions: Strengths and Benefits

- **Nomenclature better reflects common parlance** (sepsis vs severe sepsis)
- **Data-driven rather than pure expert opinion**
- **Eliminating SIRS may help clinical discrimination**
    - Guides clinicians to pay more attention to **organ dysfunction**
    - Reflects **up-to-date view of pathobiology** – what distinguishes sepsis from uncomplicated infection
    - **May also decrease broad-spectrum antibiotic utilization for SIRS alone** (?)
- **More stringent definition of septic shock may allow better comparisons of septic shock cohorts across time / place**

Sepsis-3: Criticisms, Limitations and Unresolved Issues



[Editorial]

CHEST

New Sepsis Criteria

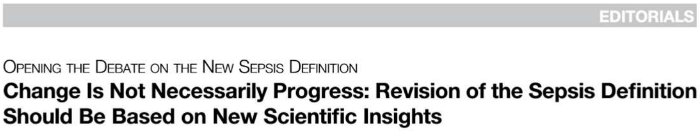
A Change We Should Not Make

Steven Q. Simpson, MD, FCCP
Kansas City, KS

CrossMark
PODCAST

there is still no known precise pathophysiological feature that defines sepsis.

The end point of the proposed criteria is increased specificity for predicting mortality or ICU stay of ≥ 3 days. Because ideal outcomes for patients result from early recognition and intervention in potentially life-threatening infection, the revised criteria may lead



EDITORIALS

OPENING THE DEBATE ON THE NEW SEPSIS DEFINITION

Change Is Not Necessarily Progress: Revision of the Sepsis Definition Should Be Based on New Scientific Insights

Criticisms: Delaying identification and treatment of serious infections?

- **Eliminating SIRS/sepsis and focusing on organ dysfunction and qSOFA may delay early identification/treatment**
  - SOFA/Sepsis and qSOFA patients are much sicker than SIRS/sepsis patients
- **New septic shock definition may be helpful for prognostic / epidemiologic purposes, but NOT helpful for clinical management**
  - Prior septic shock definition (persistent hypotension or lactate >=4.0) has important clinical implications – fluid resuscitation and timely vaospressors
- **Concerns that these changes may reverse decades of quality improvement efforts with old definitions**

Criticisms: SOFA is an unfamiliar and unwieldy clinical tool

- **SOFA initially created for ICU research**
- **Clinicians typically do not think in terms of scores**
- **Some aspects of SOFA are outdated**
  - Vasopressor scoring – no mention of vasopressin, phenylephrine; emphasis on dobutamine (not used as much for sepsis)
  - Less frequent ABGs
- **Some aspects of SOFA are ICU-specific or not routinely measured**
  - Glasgow Coma Scale
  - Vasopressor doses, P/F ratios

Other Limitations

- **No guidance on identifying infection**
- **Does not help determine if organ dysfunction is attributable to infection vs other cause**

Subjectivity likely to persist

- **Septic shock:** Some patients have shock and other organ dysfunction but never express lactate
- **Definitions do not apply to pediatrics**
- **Definitions at odds with CMS sepsis measure**
  - ➢ ***No plans from CMS to change their criteria***
    - ***CMS awaiting further data to test the utility of Sepsis-3 definitions***

Is there still a role for SIRS criteria?

- **Analysis of EHR datasets in Sepsis-3 showed that SIRS was moderately predictive of adverse outcomes**
- **Other large studies have demonstrated a stepwise increase in mortality with increasing # of SIRS[1]**
- **The mere presence of SIRS + infection carries mortality rate of 7% or more[2]**
- **SIRS + infection progresses to organ dysfunction in >50% of cases[3]**
  - ➢ ***Continued use of SIRS as (part of) a screening tool for potentially infected patients seems reasonable***

1. *Kaukonen et al, NEJM 2015*
2. *Rangel-Frausto et al, JAMA 1995*
3. *Brun-Buisson et al, Intensive Care Med 2000*

Is qSOFA the best screening tool?

- **qSOFA has high predictive ability / discrimination for poor outcomes, but has low sensitivity (30%) for detecting organ dysfunction[1]**
- **Other established early warning tools (MEWS, NEWS) appear to be better (higher AUC) at predicting mortality and/or prolonged ICU stay than qSOFA[2]**
  - SIRS criteria met earlier in hospitalization than qSOFA

➢ ***Prospective studies comparing different early warning tools (and impact on clinical outcomes) are sorely needed***

1. *Williams et al, Chest 2016*
2. *Churpek et al, Am J Resp Crit Care Med 2016*

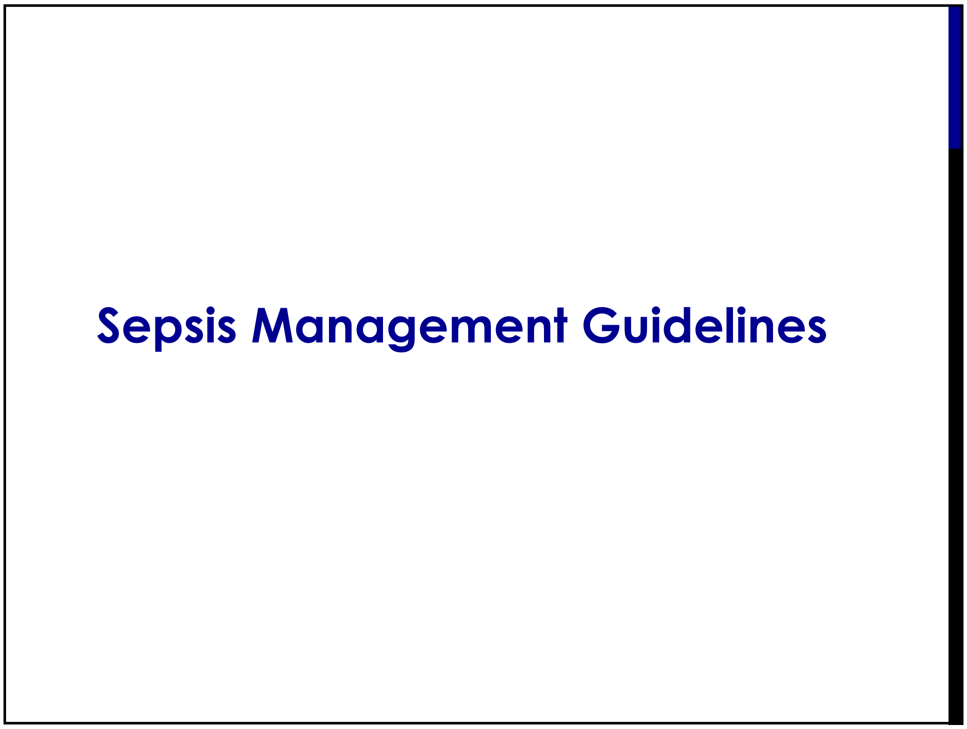
How do we diagnose infection?

Nothing new offered in Sepsis-3 definitions

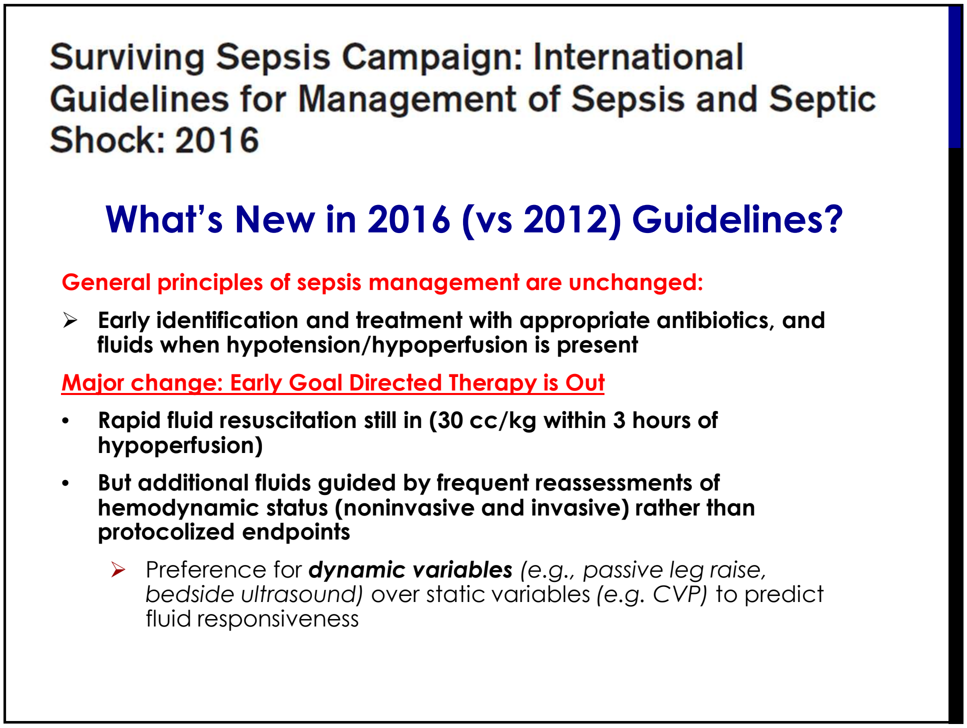
General guidance:

- ✓ **Blood Cultures**
- ✓ **Site-specific diagnostic tests / cultures and imaging**
- ✓ **Biomarkers?**
  - None are accurate enough to perfectly diagnose sepsis
  - **Procalcitonin** – imperfect but potentially useful biomarker
    - ➢ **Not sensitive enough to use to rule out sepsis in early stages, but can help guide subsequent decision to stop antibiotics once patient improving and/or alternate diagnosis becomes apparent**

Up to 50% of sepsis cases never have an organism identified



Sepsis Management Guidelines



Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

What's New in 2016 (vs 2012) Guidelines?

General principles of sepsis management are unchanged:

- **Early identification and treatment with appropriate antibiotics, and fluids when hypotension/hypoperfusion is present**

Major change: Early Goal Directed Therapy is Out

- **Rapid fluid resuscitation still in (30 cc/kg within 3 hours of hypoperfusion)**
- **But additional fluids guided by frequent reassessments of hemodynamic status (noninvasive and invasive) rather than protocolized endpoints**
    - Preference for ***dynamic variables*** *(e.g., passive leg raise, bedside ultrasound)* over static variables *(e.g. CVP)* to predict fluid responsiveness

The CMS Sepsis Measure:
Time is of the Essence

THREE HOURS

1. Measure lactate level
2. Blood cultures prior to antibiotics
3. Broad spectrum antibiotics

1 Hour Recommended by Surviving Sepsis Campaign

If hypotensive:

4. Fluid bolus (30 cc/kg NS or LR)

SIX HOURS

5. Remeasure lactate if initial lactate elevated (>2.0 mmol/L)*

For Septic Shock With Persistent Hypotension After Fluid Challenge:

6. Vasopressors to target MAP ≥ 65 mmHg
7. Repeat volume status and tissue perfusion assessment*

Also: Source Control

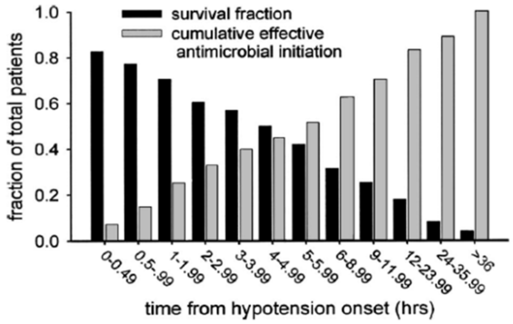
Why Check Lactates?

- **Can identify tissue hypoperfusion**
  - Often precedes overt hypotension
- **Prognostication/Risk stratification**
  - Both initial level and "lactate clearance" highly correlated with outcomes
- **Lactate clearance can be used as therapeutic target for fluid resuscitation**
- **Early, rapid lactate testing in patients with suspected sepsis associated with improved outcomes**

Shapiro et al, Ann Emerg Med 2005
Trzeciak et al, Intensive Care Med 2007
Jones et al, JAMA 2010
Singer et al, Am J Emerg Med 2014

Importance of Early Antibiotics in Sepsis

Retrospective analysis of 2731 adults in 14 ICUs with septic shock Each hour delay in antibiotics after hypotension onset associated with survival decrease of 7.6%



Kumar et al, Crit Care Med 2006, 34:1589-96.

- Similar findings in animal studies and observational studies (including severe sepsis, not just septic shock)[1,2]

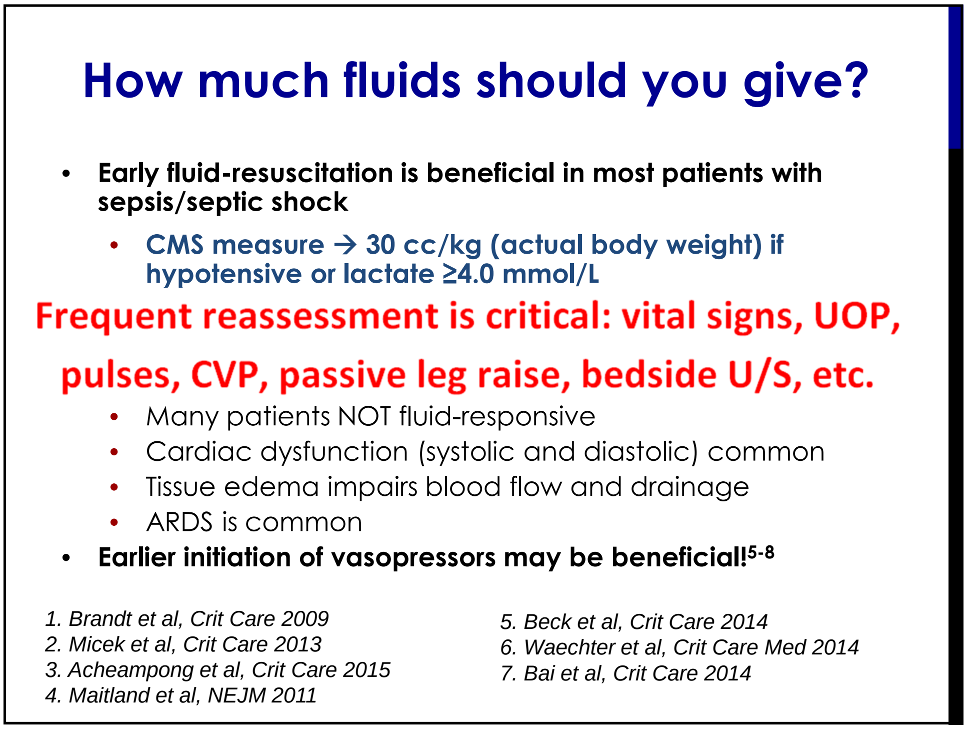
1. Gaieski et al, Crit Care Med 2010
2. Ferrer et al, Crit Care Med 2014

What are appropriate antibiotics?

Depends on specific patient: site of infection and risk of multi-drug resistant organisms

But generally prioritize as follows:

- **#1: Broad-spectrum beta-lactam**
    - Ceftriaxone, Cefepime, Piperacillin/Tazobactam, Carbapenem
- **#2: Gram-positive coverage**
    - Vancomycin, Linezolid, Daptomycin
- **+/- #3: Anaerobic Coverage** (Metronidazole - if concerned for intraabdominal process)
- **+/- #4: Antifungal** (i.e., Micafungin)



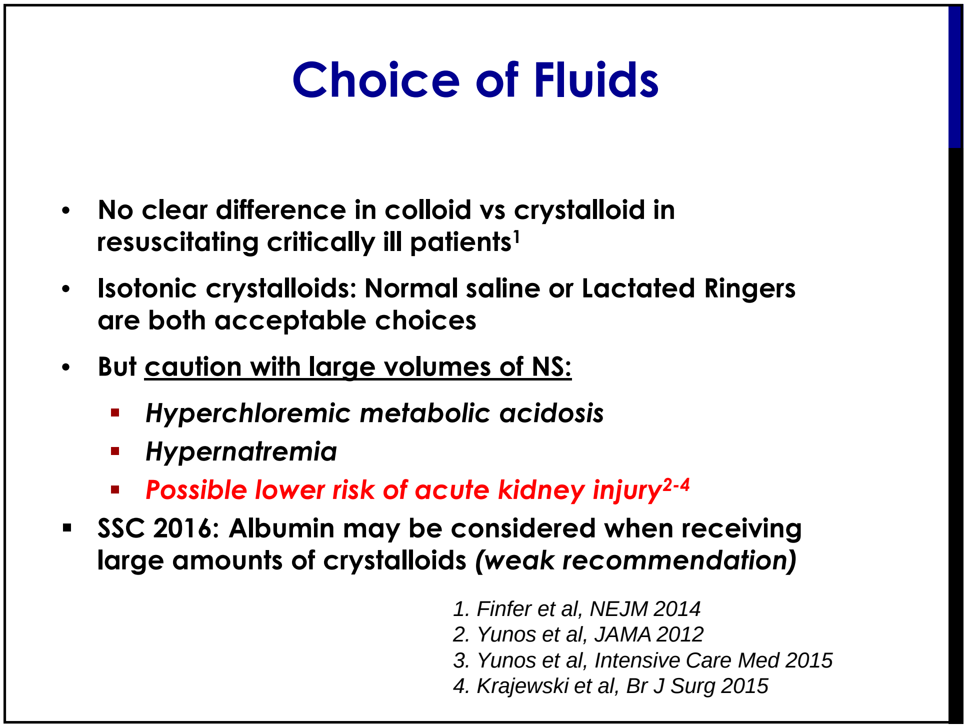
How much fluids should you give?

- **Early fluid-resuscitation is beneficial in most patients with sepsis/septic shock**
  - **CMS measure → 30 cc/kg (actual body weight) if hypotensive or lactate ≥4.0 mmol/L**

Frequent reassessment is critical: vital signs, UOP, pulses, CVP, passive leg raise, bedside U/S, etc.

  - Many patients NOT fluid-responsive
  - Cardiac dysfunction (systolic and diastolic) common
  - Tissue edema impairs blood flow and drainage
  - ARDS is common
- **Earlier initiation of vasopressors may be beneficial![5-8]**

1. Brandt et al, Crit Care 2009
2. Micek et al, Crit Care 2013
3. Acheampong et al, Crit Care 2015
4. Maitland et al, NEJM 2011
5. Beck et al, Crit Care 2014
6. Waechter et al, Crit Care Med 2014
7. Bai et al, Crit Care 2014



Choice of Fluids

- **No clear difference in colloid vs crystalloid in resuscitating critically ill patients[1]**
- **Isotonic crystalloids: Normal saline or Lactated Ringers are both acceptable choices**
- **But caution with large volumes of NS:**
  - ***Hyperchloremic metabolic acidosis***
  - ***Hypernatremia***
  - ***Possible lower risk of acute kidney injury[2-4]***
- **SSC 2016: Albumin may be considered when receiving large amounts of crystalloids *(weak recommendation)***

1. Finfer et al, NEJM 2014
2. Yunos et al, JAMA 2012
3. Yunos et al, Intensive Care Med 2015
4. Krajewski et al, Br J Surg 2015

Vasopressors

1st-line = Norepinephrine

- **SOAP-2 Trial: Equivalent outcomes vs dopamine in shock (mostly septic), but more tachyarrhythmias with dopamine[1]**

2nd-line:

- **Vasopressin (generally only as adjunct to norepinephrine)**
- **Epinephrine**

3rd-line:

- **Dopamine (beware tachyarrhythmias – very common)**
- **Phenylephrine**
  - Reflex bradycardia – useful for a-fib patients
  - Negative inotrope – avoid in heart failure

1. De Backer et al, NEJM 2010

What MAP Should We Target?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D., for the SEPSISPAM Investigators*

- Multicenter RCT in 29 French hospitals
- **776 adults with septic shock randomized to MAP target of 80-85 vs 65-70 mmHg using vasopressors**
- **No difference in 28-day mortality (or 90-day mortality)**
  - **More renal failure** with low MAP target group in patients with chronic hypertension
  - But higher incidence of **new a-fib** in the high MAP group

➢ **Classic MAP goal ≥65 still adequate for most patients**

Inotropes?

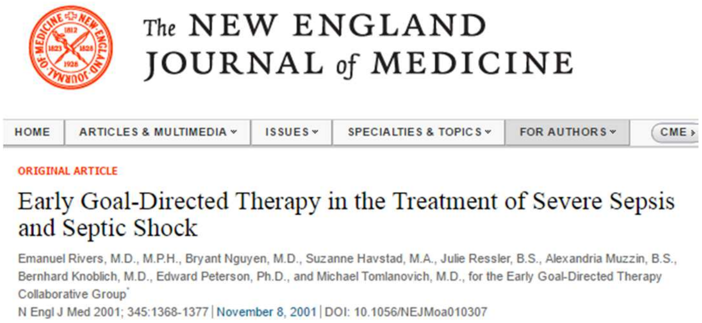
Dobutamine:

- Inotrope that can be useful if cardiogenic component
- But use with caution due to **potential for vasodilation and worsened hypotension**
- ***Diminished role in the post-Early Goal Directed Therapy era (no longer focused on achieving normal ScVO2)***

Corticosteroids?

- **Evidence is equivocal, but CORTICUS (NEJM 2007) suggested that stress dose steroids hasten reversal of shock but do not improve survival; may increase superinfection risk.**
- **SSC Guidelines continue to make weak recommendation to administer Hydrocortisone 50 mg IV q6 hours if "refractory septic shock."**
    - Alternate dose: HC 100 mg q8 hrs
- ***In practice, if patient is requiring 2 or more pressors, I give steroids***
    - Most definitely give if history of recent steroid use – potential for adrenal insufficiency

The Demise of Early Goal Directed Therapy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CME

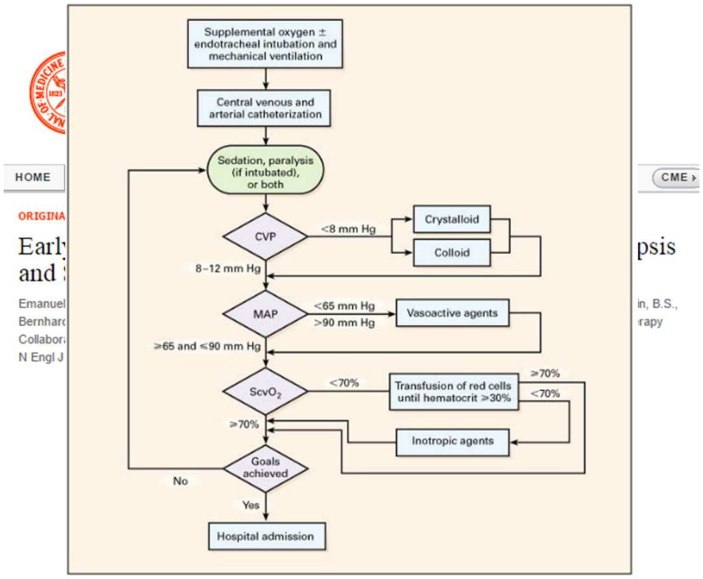
ORIGINAL ARTICLE

Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

Emanuel Rivers, M.D., M.P.H., Bryant Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandria Muzzin, B.S., Bernhard Knoblich, M.D., Edward Peterson, Ph.D., and Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group*

N Engl J Med 2001; 345:1368-1377 | November 8, 2001 | DOI: 10.1056/NEJMoa010307

→ Absolute mortality reduction of 16% (30.5% vs 46.5%)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Bernhard
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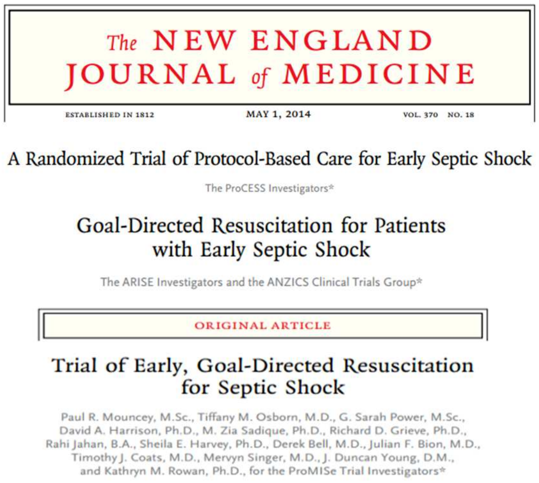
Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO$_2$
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

→ Absolute mortality reduction of 16% (30.5% vs 46.5%)

Caveats to Rivers' EGDT Study

- **Single center study**
- **Relatively small (263 patients)**
- **Unclear which parts of the protocol were really important**
- (Allegations of questionable data analysis)

→ In the current era, is the entire protocol still necessary?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

3 multi-national trials (United States, Australia / New Zealand, United Kingdom) all showed ***no difference in outcomes with EGDT vs usual care***

EGDT: Why No Benefit?

Theory #1: The original Rivers EGDT trial was bogus

Theory #2: Patients were sicker in Rivers cohort

- But no benefit in new trials even in sickest subset

Theory #3: Usual care has improved since pre-Rivers era!

- **Patients individually randomized (vs cluster-randomization) – same clinicians administering EGDT and usual care**

Concept of early aggressive therapy now ingrained in clinicians?

- ProCESS: 76% of patients received antibiotics by randomization and 97% by 6 hours
- ARISE – IV antibiotics at median of 70 minutes from ED presentation
- ProMISe – all received fluids and antibiotics before randomization

→ Early recognition and treatment with antibiotics and fluids are the key!

(Routine CVP, ScVo2 monitoring, etc. not necessary)

Summary and Take-Home Points

Epidemiology

- Sepsis is a major cause of morbidity and mortality, and is now the focus of national quality measures
- However, accurately tracking sepsis rates and outcomes is challenging

Definitions and Diagnosis

- New "definitions" shift emphasis from SIRS to qSOFA and organ dysfunction
- The new definitions have not yet been universally embraced, and concerns have been raised about potentially delaying early identification/treatment of serious infections
- Identifying infection is still the biggest challenge

Management Guidelines

- Early recognition, appropriate antibiotics, and resuscitation are still the key
- Too much fluids, though, may be harmful – earlier vasopressors are probably beneficial
- Strict adherence to Early Goal-Directed Therapy not needed → more emphasis on frequent reassessments using static and dynamic measures of fluid-responsiveness

Question 1

Which is the following is FALSE regarding the new Sepsis-3 definitions?

a) Sepsis-associated organ dysfunction can be quantified by a rise in the Sequential Organ Failure Assessment score by 2 or more from baseline

b) Septic shock is defined as infection leading to persistent hypotension requiring vasopressors, AND an elevated lactate of >2 mmol/L in the absence of fluid resuscitation

c) The systemic inflammatory response syndrome criteria are no longer part of the definition of sepsis

d) The quick SOFA criteria replace SIRS in the new definition of sepsis

e) The quick SOFA criteria were developed and validated in large EHR datasets based on their ability to predict death and/or prolonged ICU stay in patients with suspected infection

Question 1

Which is the following is FALSE regarding the new Sepsis-3 definitions?

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b) Septic shock is defined as infection leading to persistent hypotension requiring vasopressors, AND an elevated lactate of >2 mmol/L in the absence of fluid resuscitation

c) The systemic inflammatory response syndrome criteria are no longer part of the definition of sepsis

d) The quick SOFA criteria replace SIRS in the new definition of sepsis

- Rationale: qSOFA is meant to serve as simple, efficient prompt for patients who are at high risk for adverse outcomes. However, not all patients with sepsis will meet qSOFA criteria (unlike the traditional definitions of sepsis, which required SIRS criteria)

e) The quick SOFA criteria were developed and validated in large EHR datasets based on their ability to predict death and/or prolonged ICU stay in patients with suspected infection

Question 2

A 65 year old female with diabetes, hypertension, and kidney stones, who weighs 80 kg, presents to the emergency department with several days of fevers, flank pain, dysuria, and malaise. She is tachycardic, confused, tachypneic, and hypotensive with a systolic blood pressure of 70/40. Initial lactate (drawn shortly after presentation) is 2.5 mmol/L. She is given ceftriaxone (after blood cultures) within 3 hours of arrival. She is bolused with 2 liters of normal saline within 2 hours of arrival, with improvement in her hypotension. One hour after finishing her 2nd liter fluid bolus, she becomes hypotensive again to 70/40.

Which of the following is true, with regards to her care and the CMS SEP-1 measure?

a) To pass the SEP-1 measure, she should be started on vasopressors within 3 hours of her recurrent hypotension

b) The amount of fluids she received is inadequate to pass the SEP-1 measure

c) Her care fails the SEP-1 measure because antibiotics were not given within 1 hour of sepsis presentation

d) She does not meet severe sepsis criteria for the SEP-1 measure

e) Based on her initial lactate level, a repeat lactate level is not required

Question 2

Which of the following is true, with regards to her care and the CMS SEP-1 measure?

a) To pass the SEP-1 measure, she should be started on vasopressors within 3 hours of her recurrent hypotension. FALSE: the SEP-1 measure requires vasopressor initiation within 6 hours of recurrent hypotension (septic shock)

b) The amount of fluids she received is inadequate to pass the SEP-1 measure. TRUE: the SEP-1 measure requires 30 cc/kg of fluids within 3 hours of sepsis-associated hypotension. In this case, that would have been 2.4 liters.

c) Her care fails the SEP-1 measure because antibiotics were not given within 1 hour of sepsis presentation. FALSE: the SEP-1 measure requires antibiotics to be given within 3 hours of severe sepsis presentation.

d) She does not severe sepsis criteria for the SEP-1 measure. FALSE: she has SIRS criteria, suspected infection, and organ dysfunction (based on her hypotension and elevated lactate).

e) Based on her initial lactate level, a repeat lactate level is not required. FALSE: a repeat lactate is required within 6 hours if the initial lactate is >2.0 mmol/L.

Questions?

Chanu Rhee (crhee@bwh.harvard.edu)

Key References

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1. C.W. Seymour, V.X. Liu, T.J. Iwashyna, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), JAMA 315(8) (2016) 762-74.

2. M. Shankar-Hari, G.S. Phillips, M.L. Levy, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), JAMA 315(8) (2016) 775-87.

3. M. Singer, C.S. Deutschman, C.W. Seymour, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), JAMA 315(8) (2016) 801-10.

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U.S. Early Goal-Directed Therapy Trial:

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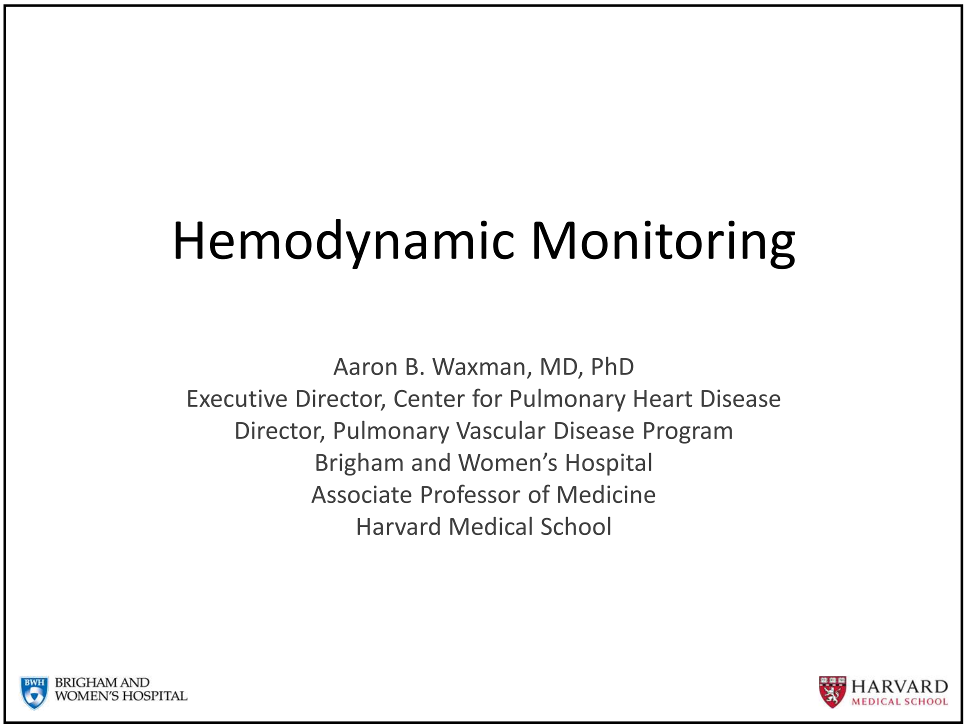

Hemodynamic Monitoring

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Director, Pulmonary Vascular Disease Program
Brigham and Women’s Hospital
Associate Professor of Medicine
Harvard Medical School

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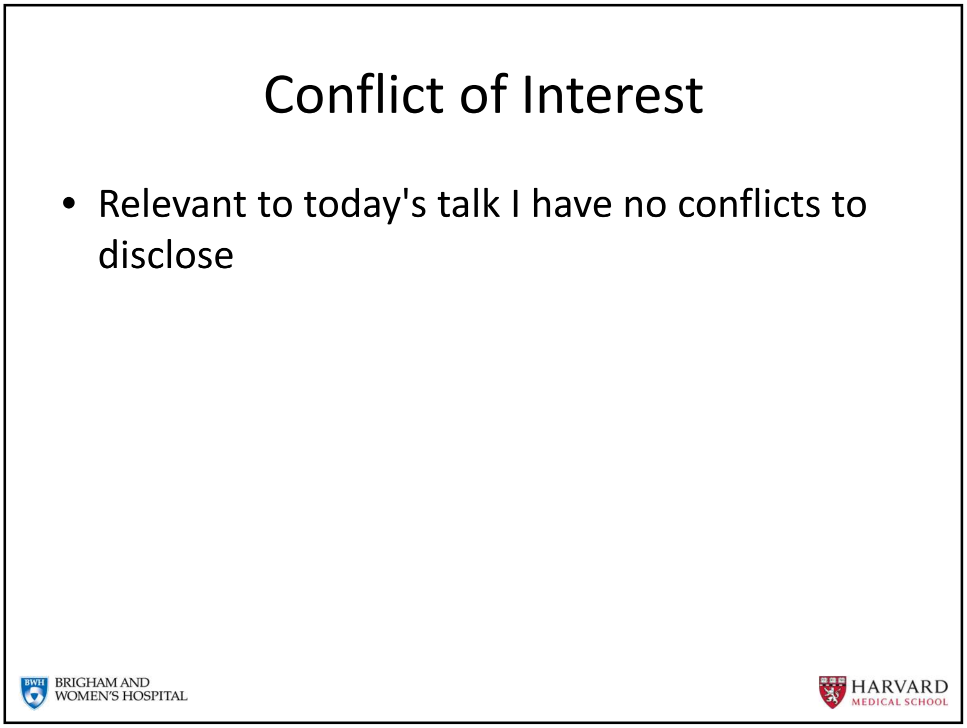

Conflict of Interest

- Relevant to today's talk I have no conflicts to disclose

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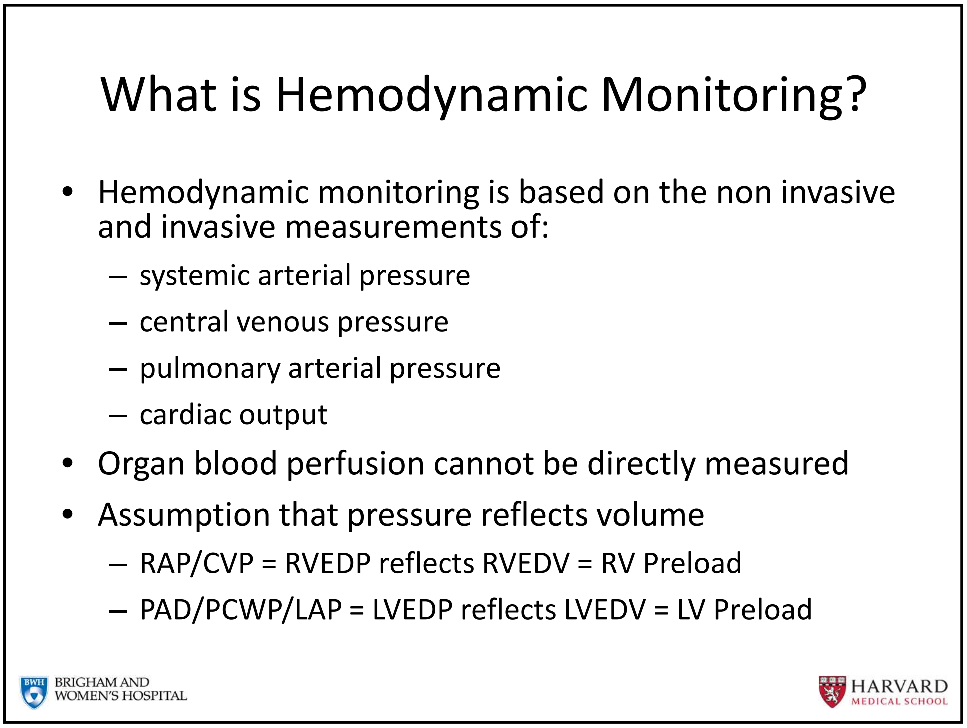

What is Hemodynamic Monitoring?

- Hemodynamic monitoring is based on the non invasive and invasive measurements of:
  - systemic arterial pressure
  - central venous pressure
  - pulmonary arterial pressure
  - cardiac output
- Organ blood perfusion cannot be directly measured
- Assumption that pressure reflects volume
  - RAP/CVP = RVEDP reflects RVEDV = RV Preload
  - PAD/PCWP/LAP = LVEDP reflects LVEDV = LV Preload

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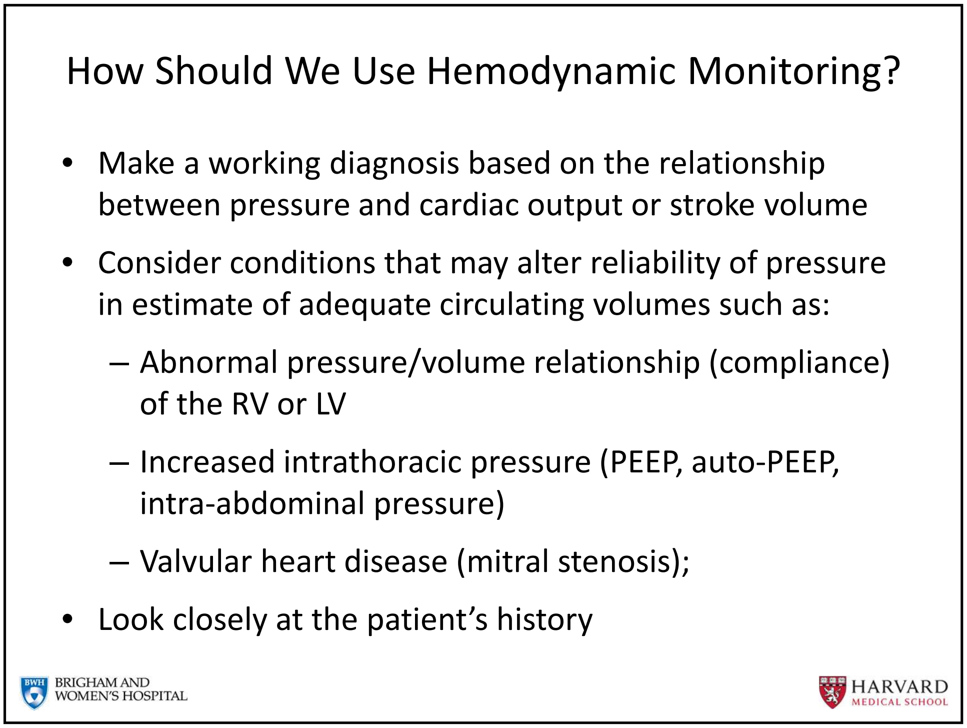

How Should We Use Hemodynamic Monitoring?

- Make a working diagnosis based on the relationship between pressure and cardiac output or stroke volume
- Consider conditions that may alter reliability of pressure in estimate of adequate circulating volumes such as:
  - Abnormal pressure/volume relationship (compliance) of the RV or LV
  - Increased intrathoracic pressure (PEEP, auto-PEEP, intra-abdominal pressure)
  - Valvular heart disease (mitral stenosis);
- Look closely at the patient’s history

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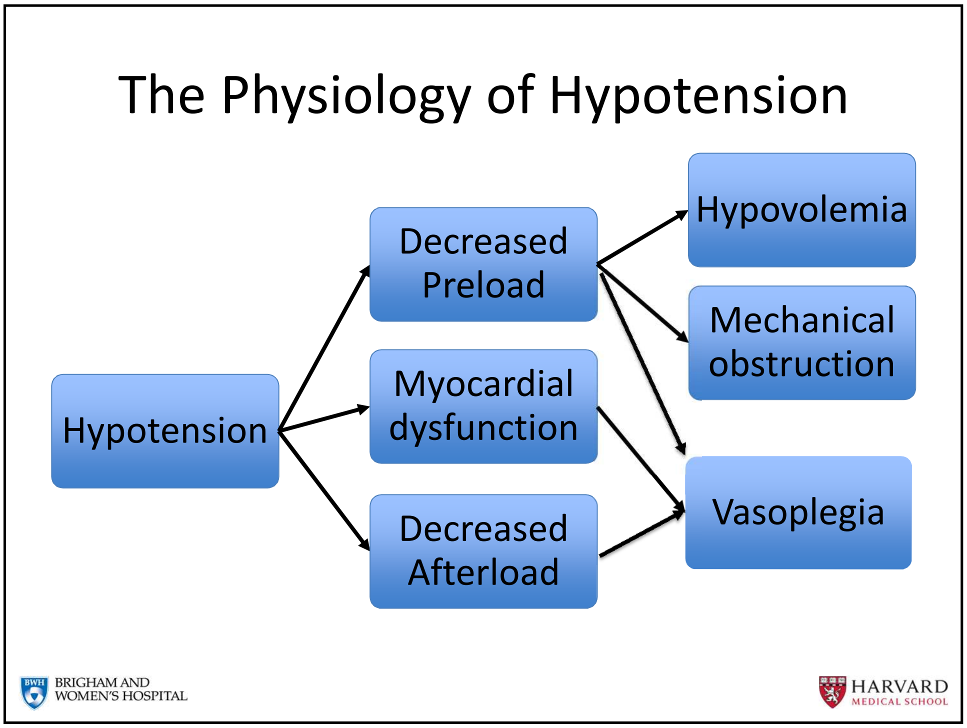

The Physiology of Hypotension

Hypotension

Decreased Preload

Myocardial dysfunction

Decreased Afterload

Hypovolemia

Mechanical obstruction

Vasoplegia

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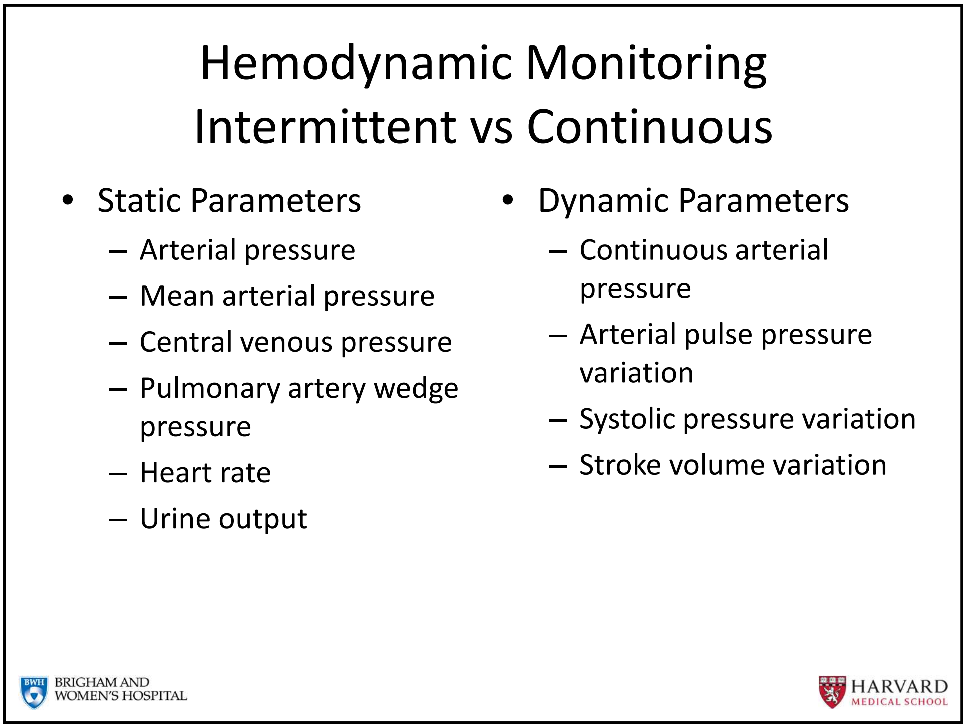

Hemodynamic Monitoring Intermittent vs Continuous

- Static Parameters
  - Arterial pressure
  - Mean arterial pressure
  - Central venous pressure
  - Pulmonary artery wedge pressure
  - Heart rate
  - Urine output
- Dynamic Parameters
  - Continuous arterial pressure
  - Arterial pulse pressure variation
  - Systolic pressure variation
  - Stroke volume variation

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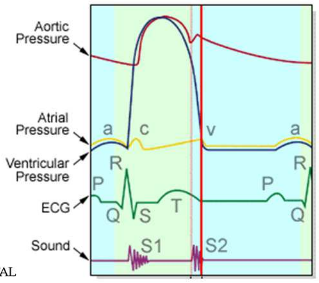
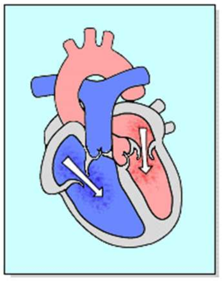
Hemodynamic Targets

- Heart rate
- Preload
- Afterload
- Contractility
- SvO_2

- Too fast / too slow
- Too high / too low
- Too high / too low
- Improve ventricular performance





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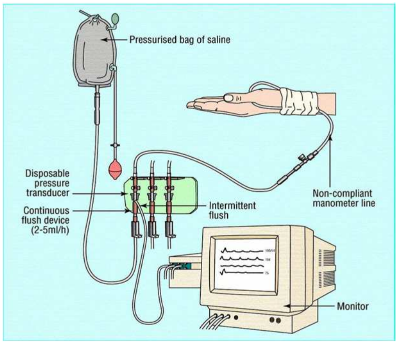
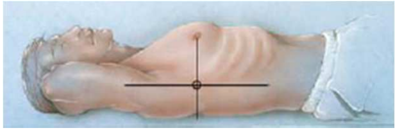
Accuracy of Hemodynamic Data

- Proper leveling
- Proper zeroing
- Eliminate hydrostatic pressure differences within fluid-filled system by zeroing system at estimated level of the catheter tip


Pressurised bag of saline
Disposable pressure transducer
Continuous flush device (2-5ml/h)
Intermittent flush
Non-compliant manometer line
Monitor



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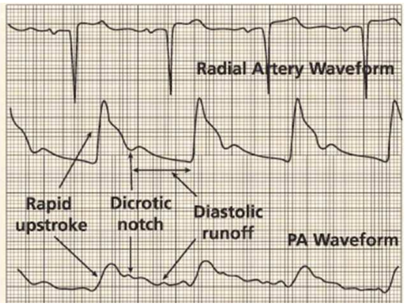
Mean Arterial Pressure

- MAP is a physiological estimate of perfusion pressure
  - Less subject to variability than systolic pressure
  - MAP ≥65 mmHg is a reasonable target
  - At times (chronic hypertension, cerebral edema, spinal cord ischemia), higher values are necessary
  - Optimal blood flow through vital organs is first achieved by maintaining adequate circulating volume
- Increase in MAP with vasoconstrictors in hypovolemic patients does not mean adequate organ perfusion

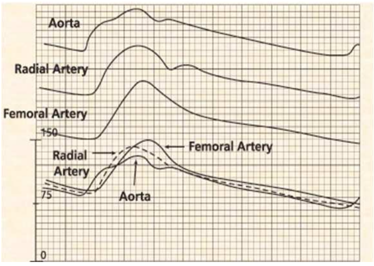
---

Arterial Pressure Monitoring

- Systemic arterial waveform is characterized by:
  - A rapid upstroke and downslope – systolic ejection
  - A dicrotic notch – closure of aortic valve
  - Smooth progressive runoff – diastole



Interpreting Arterial Waveforms



- The arterial pressure waveform changes shape and value depending on the site of measurement
  - The systolic pressure increases by as much as 20 mmHg the farther the monitoring site is from the aorta
  - The dicrotic notch of the waveform becomes less distinct the farther the monitoring site is from the aorta

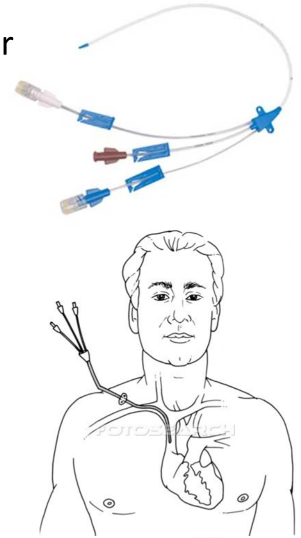
Limitations of Arterial Pressure

- 58 yo moderately obese woman, H/O DM, presents with hours of worsening SOB and delirium
- Temp: 100.7
- MAP: 57 mmHg
- HR: 117
- WBC: 4.5
- Hct: 23
- CXR: NAD

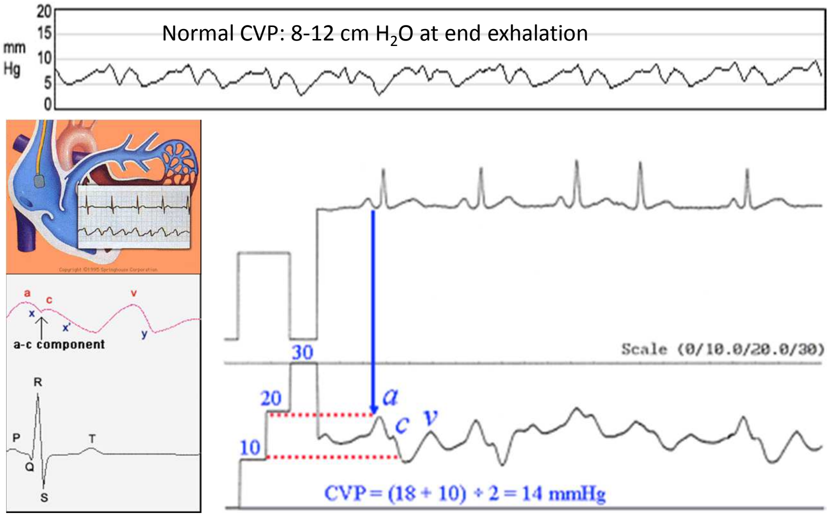
- Is this cardiogenic? Septic? Hemorrhagic?
- How much fluid should we give her?
- When should pressors be started?
- What is the best pressor to consider?

Central Venous Pressure

- CVP is often used as sole parameter to monitor hemodynamics.
- The purpose of measuring CVP / RAP is to estimate RVEDP, which reflects RVEDV
- CVP alone may not differentiate between changes in volume (different venous return curve) or changes in contractility (different Starling curve)



Normal CVP / right atrial pressure waveform is low-amplitude and undulating

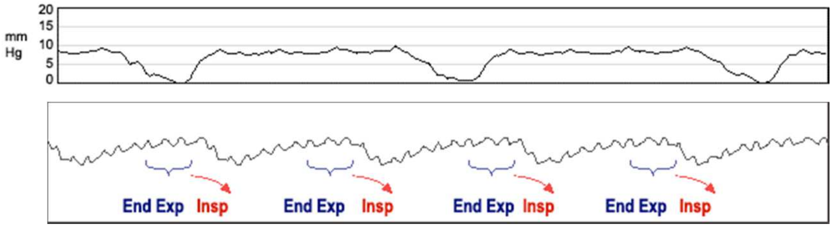


Normal CVP: 8-12 cm H_2O at end exhalation

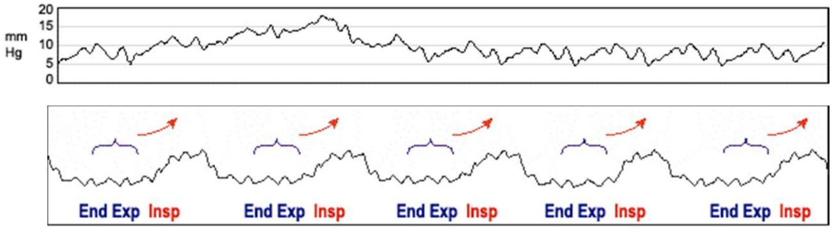
$CVP = (18 + 10) \div 2 = 14$ mmHg

CVP pressure can vary significantly with respiration

Spontaneous Ventilation:



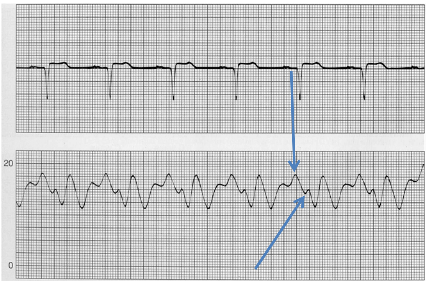
Positive Pressure Ventilation:

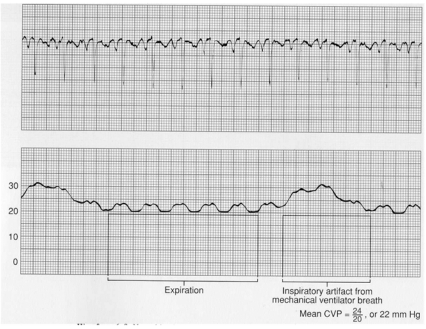


Examples of CVP measurements

Normal CVP

Patient on PPV



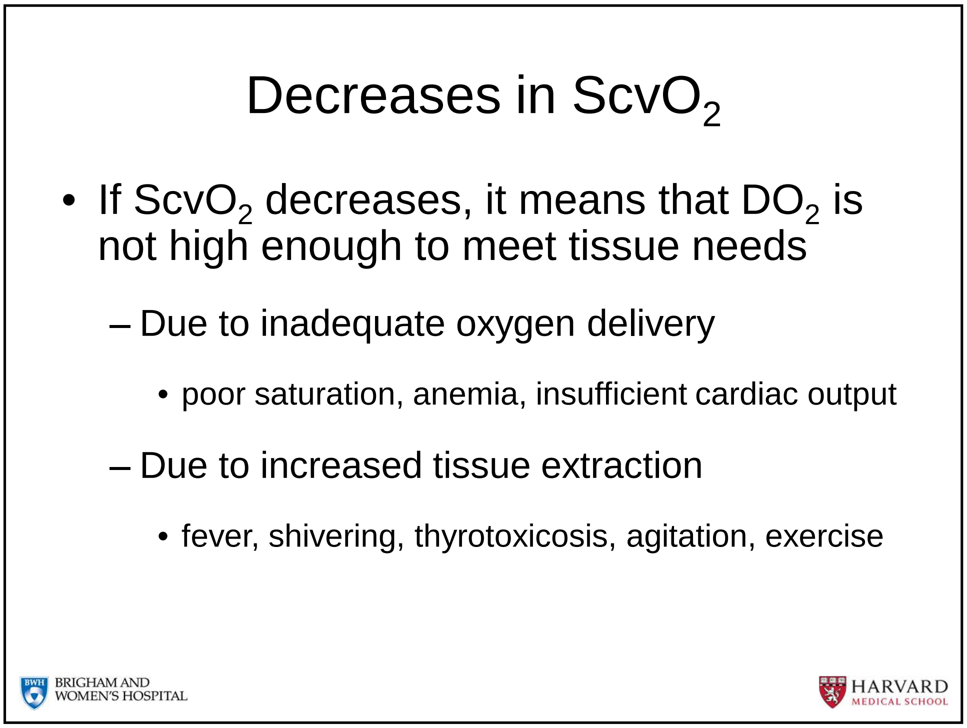

30
20
10
0
Expiration
Inspiratory artifact from mechanical ventilator breath
Mean CVP = $\frac{24}{20}$, or 22 mm Hg

What is $ScvO_2$?

- The determinants of $ScvO_2$ can be approximately defined by a modified Fick equation:
  - $SvO_2 = SaO_2 - VO_2 / 13.9 \times Q \times [Hb]$
- *So, it is affected by:*
  - Hemoglobin
  - Cardiac output
  - SaO_2
  - Tissue oxygen requirements
- Normal $ScvO_2$ ~ 68-75%

So, how do you use it?

- Changes in $ScvO_2$ should lead you to look for the *cause* of that change
  - Hemoglobin
  - Cardiac output
  - SaO_2
  - Tissue oxygen requirements
- It is important to look at the clinical picture, the whole picture, and combine that information with the data at hand



Decreases in $ScvO_2$

- If $ScvO_2$ decreases, it means that DO_2 is not high enough to meet tissue needs
  - Due to inadequate oxygen delivery
    - poor saturation, anemia, insufficient cardiac output
  - Due to increased tissue extraction
    - fever, shivering, thyrotoxicosis, agitation, exercise

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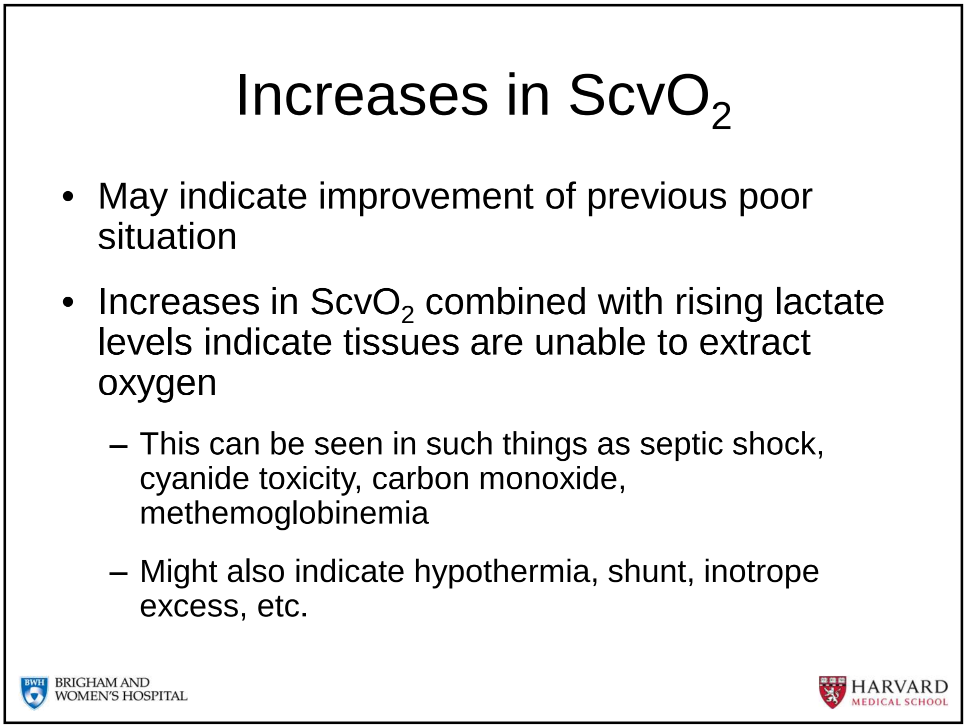

Increases in $ScvO_2$

- May indicate improvement of previous poor situation
- Increases in $ScvO_2$ combined with rising lactate levels indicate tissues are unable to extract oxygen
  - This can be seen in such things as septic shock, cyanide toxicity, carbon monoxide, methemoglobinemia
  - Might also indicate hypothermia, shunt, inotrope excess, etc.

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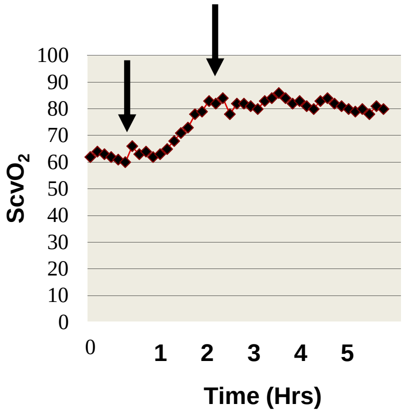
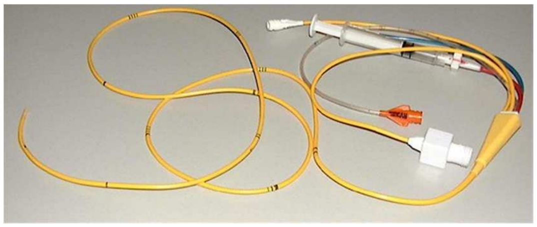
Case Study - Sepsis

- 72 year old woman
- 3 days of dysuria and new onset confusion
- T°C (39.9), HR 132, BP 82/40, and RR 33
- Lactate of 4.3
- Resuscitation started with NS



PA Catheter Uses

- To establish diagnosis
- To guide therapy
- To monitor response to therapy
- To assess determinants of oxygen delivery



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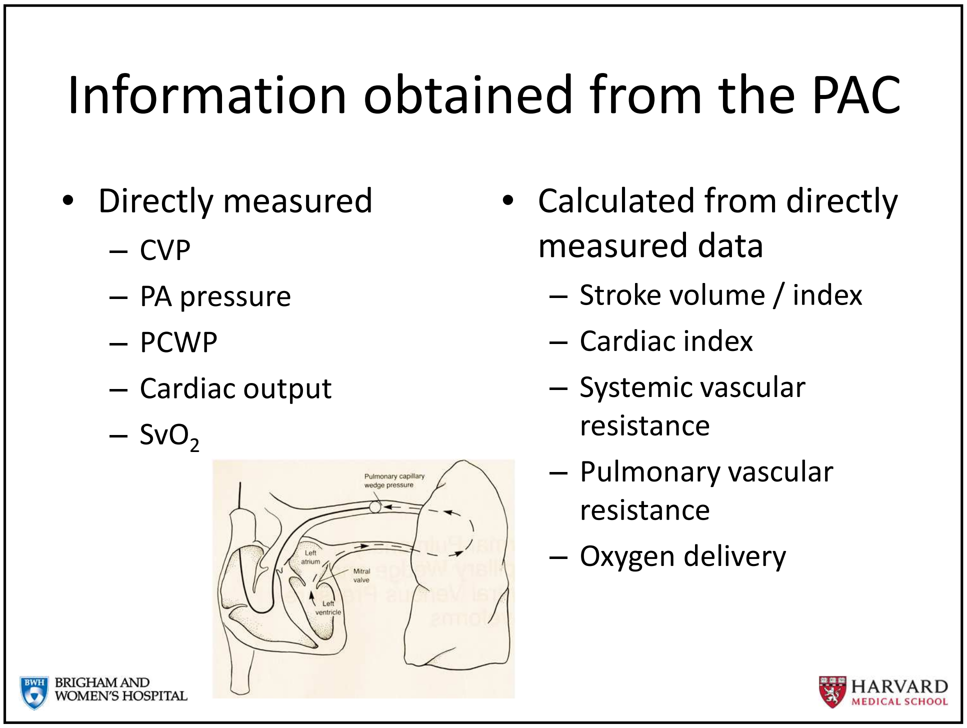

Information obtained from the PAC

- Directly measured
  - CVP
  - PA pressure
  - PCWP
  - Cardiac output
  - SvO_2
- Calculated from directly measured data
  - Stroke volume / index
  - Cardiac index
  - Systemic vascular resistance
  - Pulmonary vascular resistance
  - Oxygen delivery

Pulmonary capillary wedge pressure
Left atrium
Mitral valve
Left ventricle

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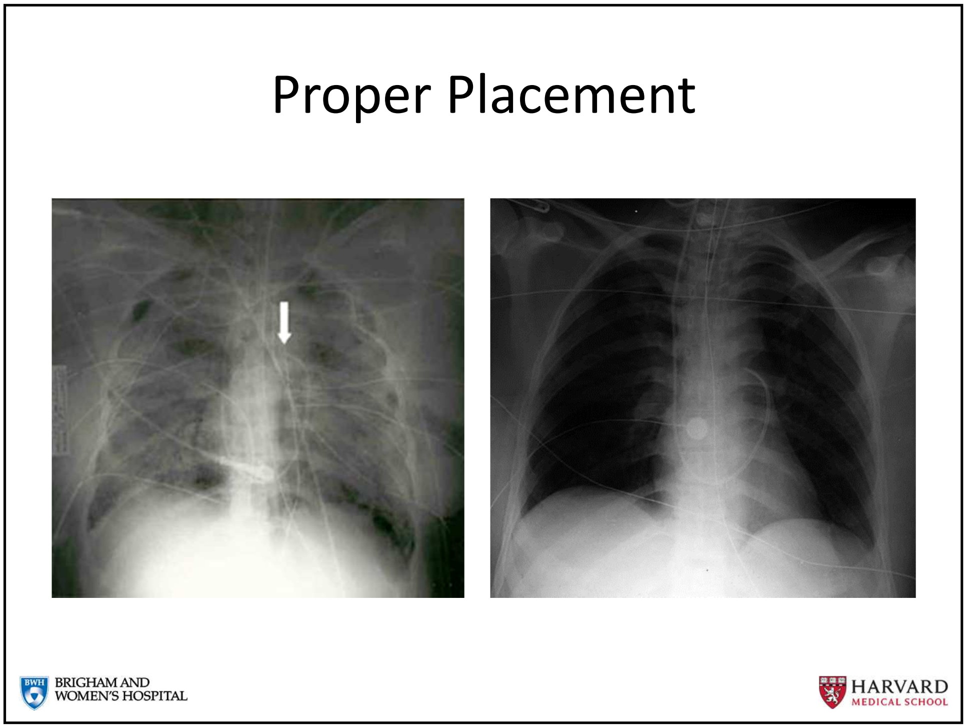

Proper Placement

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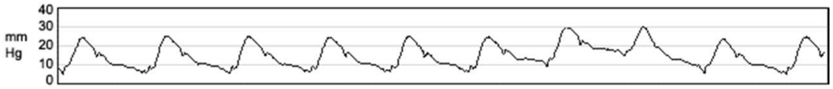
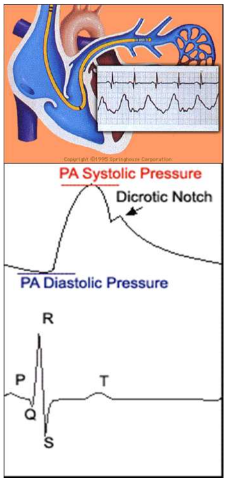
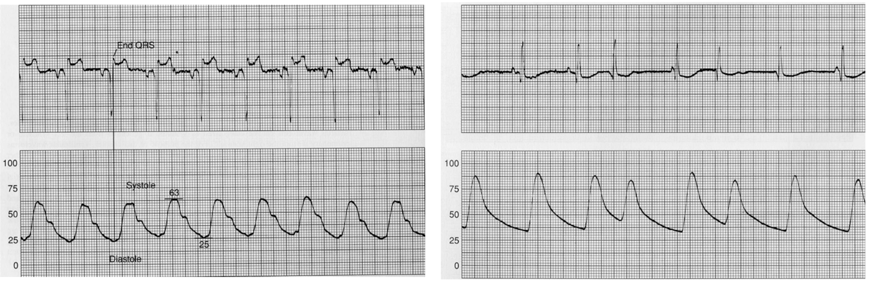
Pulmonary Artery Pressure



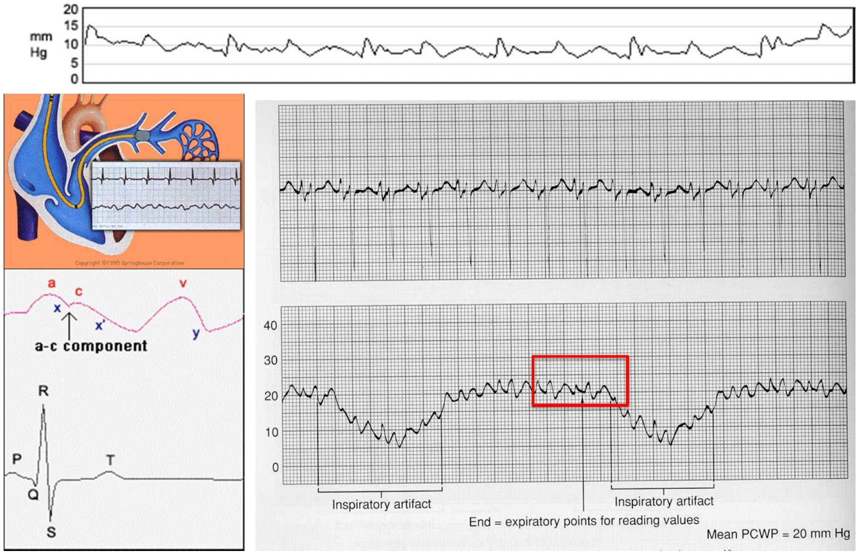

PA Systolic Pressure
Dicrotic Notch
PA Diastolic Pressure
R
P
T
Q
S

- The normal pulmonary arterial (PA) pressure waveform is pulsatile, with a sharp systolic upstroke
- Exaggeration of the dicrotic notch is commonly observed
  - Systolic pressure 15-30 mm Hg
  - Diastolic pressure 10-15 mm Hg
  - Mean pressure 10-20 mm Hg

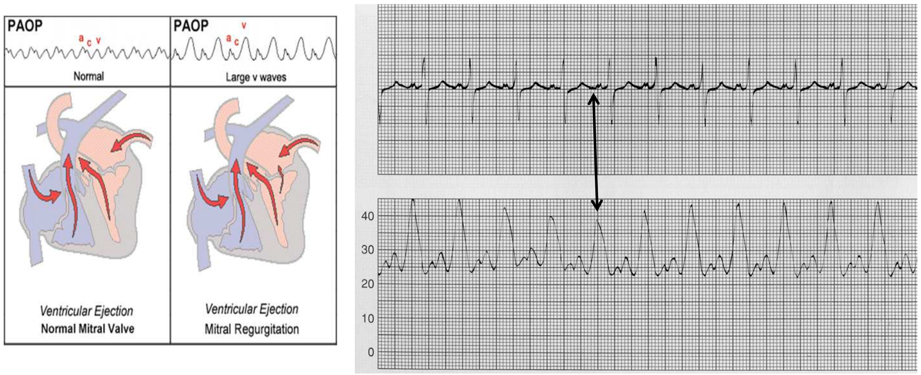
PA Pressure Tracings


End QRS
100
75
50
25
0
Systole
63
25
Diastole

Normal PCWP waveform is low amplitude and undulating

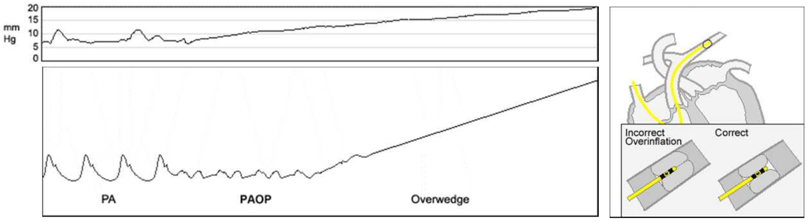


Large “v” Waves



- Large “v” waves reflect an increase in pressure during atrial filling due to
  - Retrograde flow from MR
  - Decreased atrial compliance
  - Increased flow into the LA

Overwedged



- Overwedge causes abrupt elevation and flattening of the waveform during balloon inflation
- The overwedge waveform is pulsatile until it exceeds PA systolic pressure, at which point it becomes smooth
  - True PCWP can never be greater than PA systolic pressure
- ”Overwedge” results from obstruction of the catheter tip
  - prolapse of the balloon over the tip
  - positioning of the distal port against the vessel wall
  - development of a thrombus
- With catheter tip occlusion, continuous infusion of fluid rapidly elevates pressure

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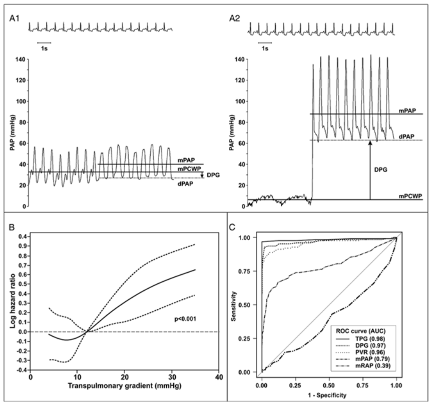
Pulmonary Vascular Resistance



- Transpulmonary gradient:
  - mPA-PCWP
  - 12-15
  - PVR=TPG/CO
- Diastolic pressure gradient:
  - PAD-PCWP
  - ≤ 7

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Chest. 2013;143(3):758-766

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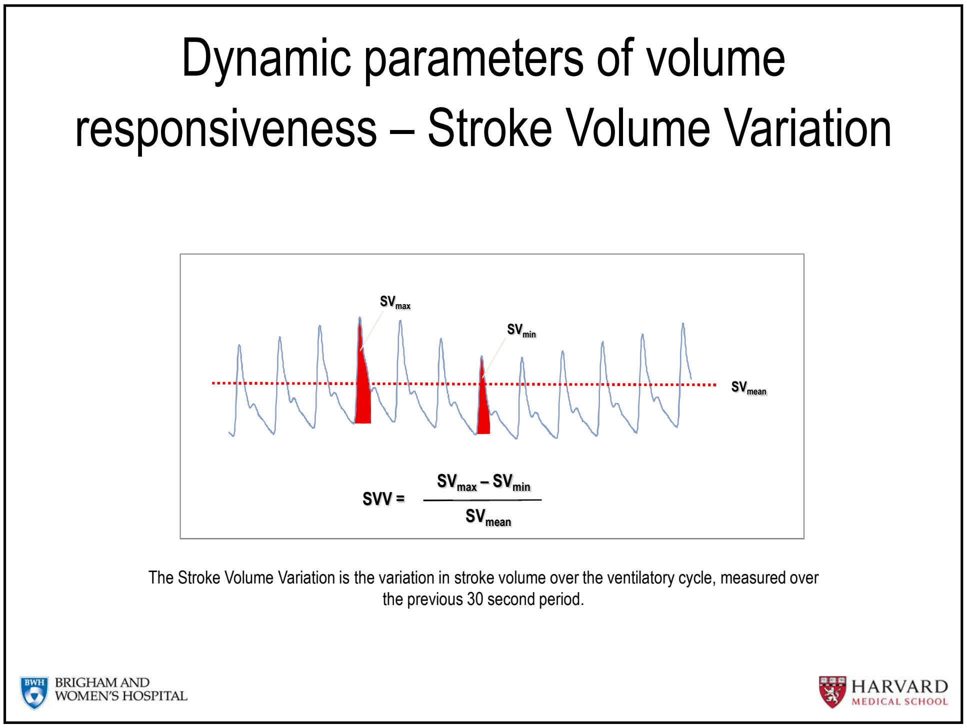
Key Question Answered by the RHC

- 37 yo moderately obese woman presents with DOE, worsening lower extremity edema and RVSP estimated at 72 mmHg with no mention of the RV and

Mild enlargement of RA, Normal LV	Mild enlargement of the LA, mild LVH	Mild enlargement of the LA with mild LVH
RA: 11	RA: 11	RA: 11
RV: 87/3 RVEDP: 12	RV: 87/3 RVEDP: 12	RV: 87/3 RVEDP: 12
PA: 77/34	PA: 77/34	PA: 77/34
mPA: 48	mPA: 48	mPA: 48
PCWP: 9	**PCWP: 27**	**PCWP: 39**
TPG: 39	TPG: 21	TPG: 9
SvO_2: 67%	SvO2: 67%	SvO2: 67%
CO: 3.6L/min	CO: 3.6 L/min	CO: 3.6 L/min
PVR: 10.8	PVR: 5.8	PVR: 2.5

Dynamic Assessment of Intravascular Volume

- CVP change to fluid challenge
- IVC/SVC Caliber changes in response to breathing
- Stroke Volume Variation (SVV)
- Pulse Pressure Variation (PPV)
- Dynamic Changes in Aortic Flow Velocity/Stroke Volume Assessed by Echocardiography



Dynamic parameters of volume responsiveness – Stroke Volume Variation

SV_{max}
SV_{min}
SV_{mean}

$$SVV = \frac{SV_{max} - SV_{min}}{SV_{mean}}$$

The Stroke Volume Variation is the variation in stroke volume over the ventilatory cycle, measured over the previous 30 second period.

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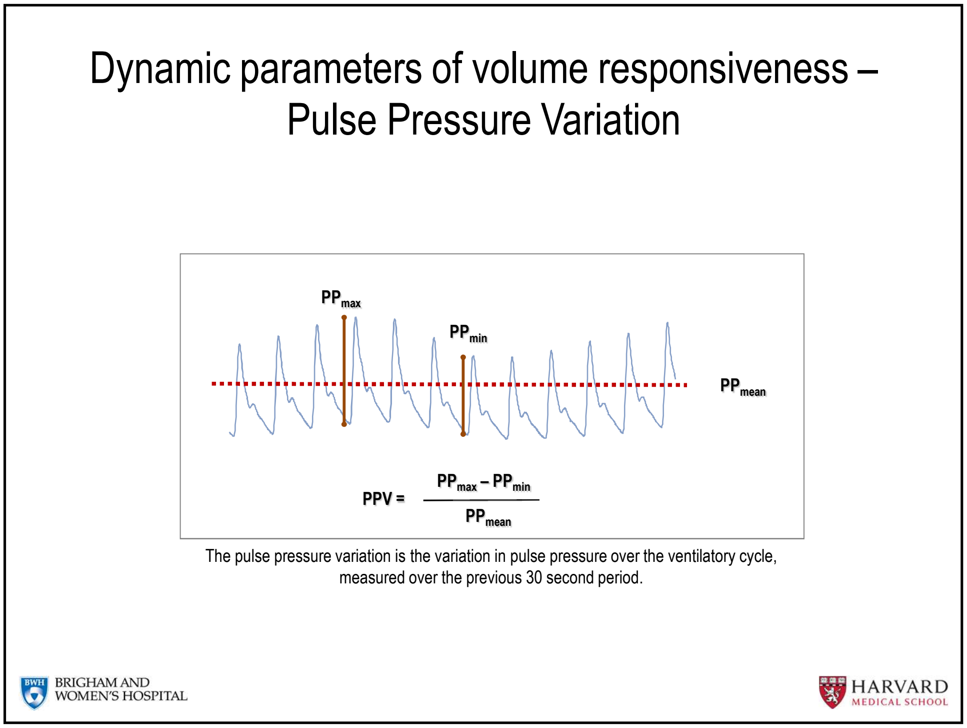

Dynamic parameters of volume responsiveness – Pulse Pressure Variation

PP_{max}
PP_{min}
PP_{mean}

$$PPV = \frac{PP_{max} - PP_{min}}{PP_{mean}}$$

The pulse pressure variation is the variation in pulse pressure over the ventilatory cycle, measured over the previous 30 second period.

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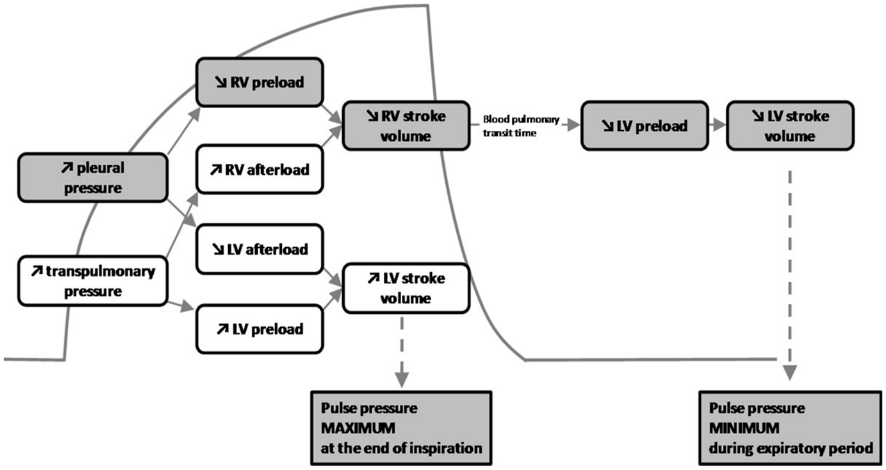
Limitations of the respiratory variation in stroke volume for predicting fluid responsiveness

- When a patient has some breathing efforts under mechanical ventilation – and even more when the patient is not intubated
- Cardiac arrhythmias
- Conditions in which the variations in intravascular pressure induced by mechanical ventilation are of small amplitude like low tidal volumes
- If the ratio of heart rate to respiratory rate is low, e. g., if the respiratory rate is elevated, the number of cardiac cycles per respiratory cycle may be too low to allow respiratory stroke volume variation (SVV) to occur
- Increased abdominal pressure
- Open-chest conditions

Hemodynamic Effects of Mechanical Ventilation



↗ pleural pressure

↗ transpulmonary pressure

↘ RV preload

↗ RV afterload

↘ LV afterload

↗ LV preload

↘ RV stroke volume

Blood pulmonary transit time

↘ LV preload

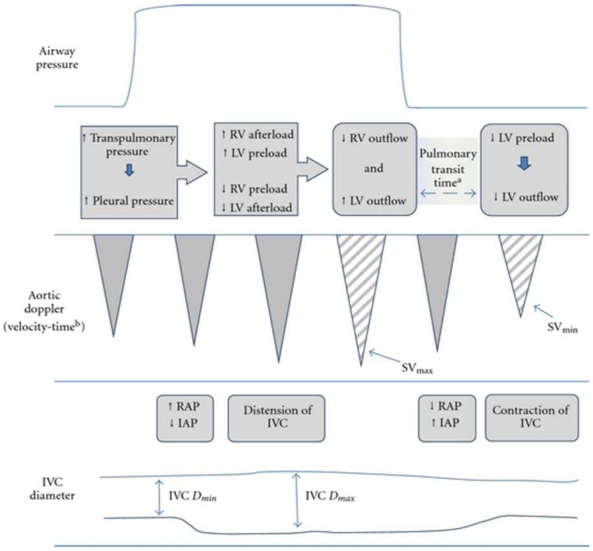
↘ LV stroke volume

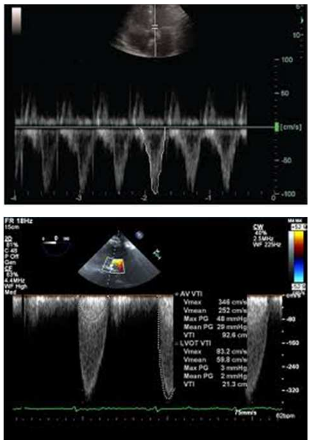
↗ LV stroke volume

Pulse pressure MAXIMUM at the end of inspiration

Pulse pressure MINIMUM during expiratory period

AORTIC VELOCITY TIME INTEGRAL AND PEAK AORTIC VELOCITIES


Airway pressure
↑ Transpulmonary pressure
↑ Pleural pressure
↑ RV afterload
↑ LV preload
↓ RV preload
↓ LV afterload
↓ RV outflow
and
↑ LV outflow
Pulmonary transit time^a
↓ LV preload
↓ LV outflow
Aortic doppler (velocity-time^b)
SV_{max}
SV_{min}
↑ RAP
↓ IAP
Distension of IVC
↓ RAP
↑ IAP
Contraction of IVC
IVC diameter
IVC D_{min}
IVC D_{max}



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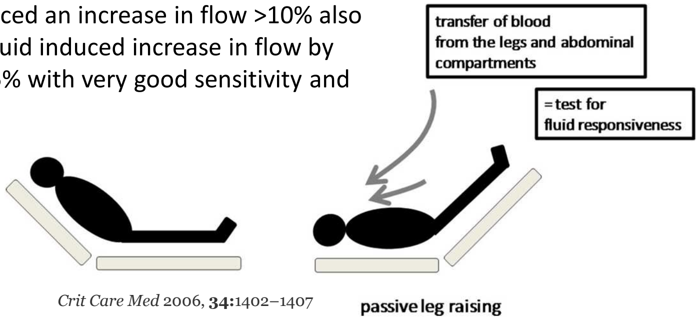
Passive Leg Raising

- PLR induced changes in stroke volume closely correlate with changes in stroke volume induced by a 300ml colloid infusion
  - Preload responsive patients may see a maximal effect within 90 seconds and will reach a 10-15% increase in stroke volume
  - PLR that induced an increase in flow >10% also predicted a fluid induced increase in flow by more than 15% with very good sensitivity and specificity


transfer of blood from the legs and abdominal compartments
= test for fluid responsiveness
passive leg raising

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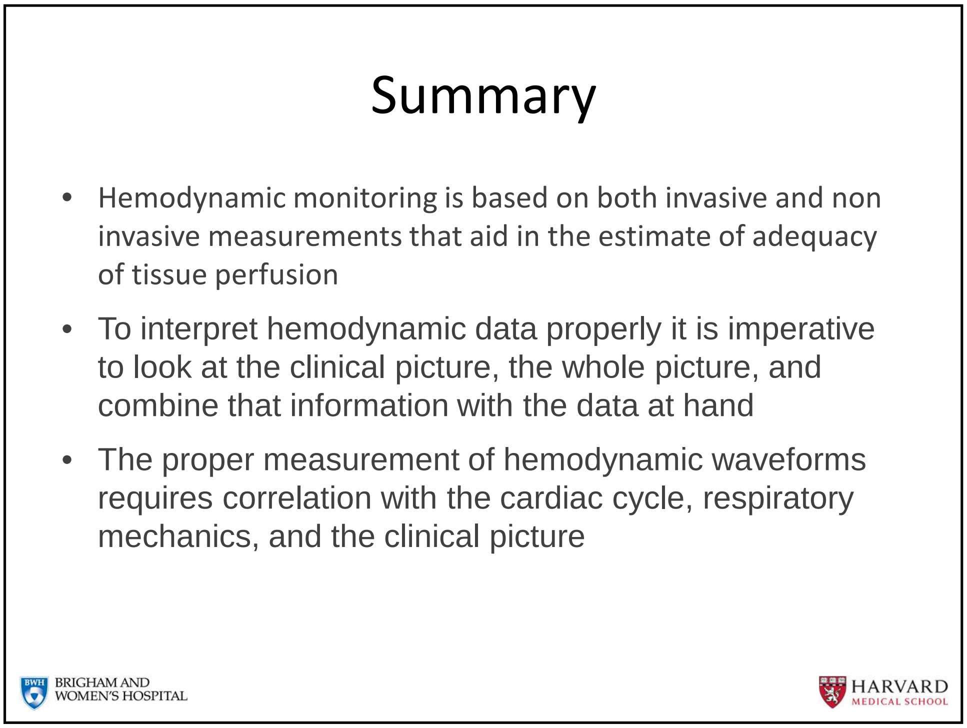
Crit Care Med 2006, **34:**1402–1407



Summary

- Hemodynamic monitoring is based on both invasive and non invasive measurements that aid in the estimate of adequacy of tissue perfusion
- To interpret hemodynamic data properly it is imperative to look at the clinical picture, the whole picture, and combine that information with the data at hand
- The proper measurement of hemodynamic waveforms requires correlation with the cardiac cycle, respiratory mechanics, and the clinical picture

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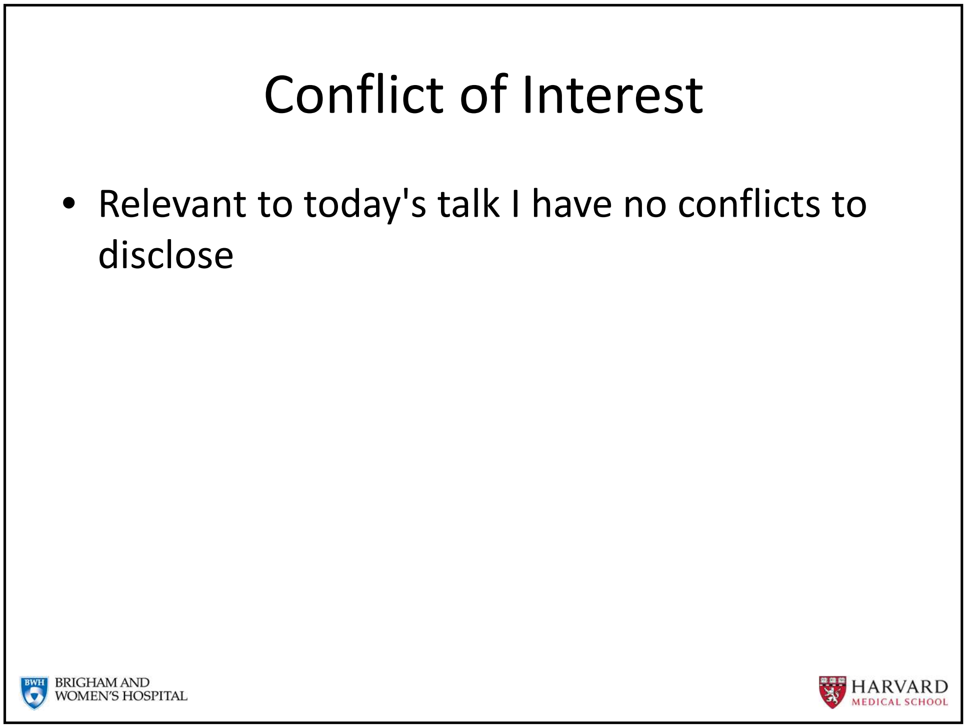

Conflict of Interest

- Relevant to today's talk I have no conflicts to disclose

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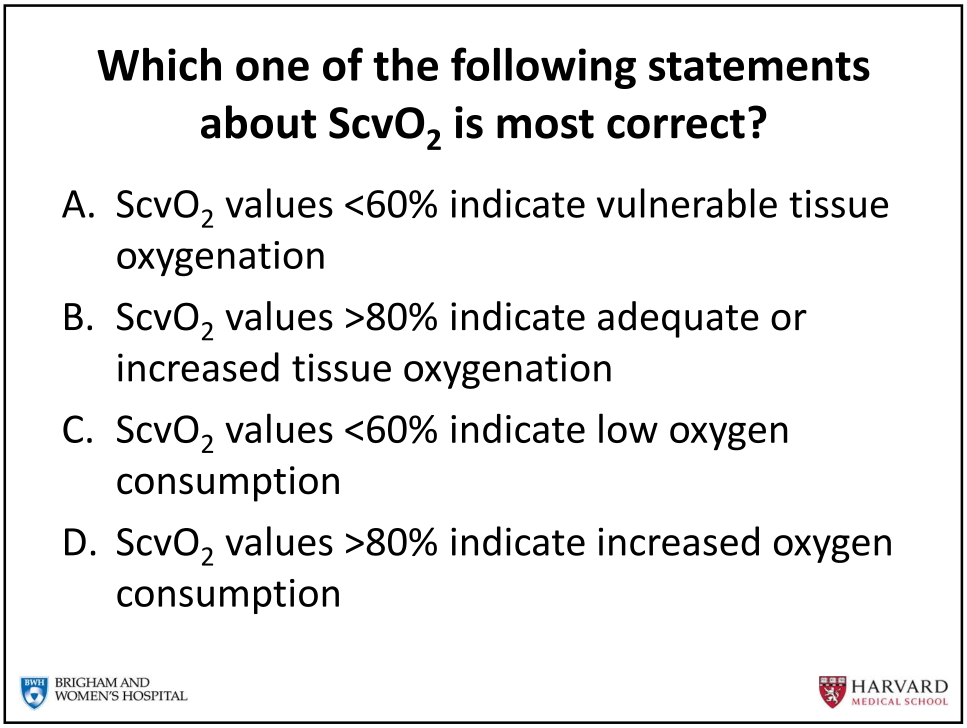
Which portion of the ventricular waveform represents the preload state?

A. Systolic peak
B. Beginning diastole
C. End diastolic pressure
D. The ventricular upstroke

Which portion of the ventricular waveform represents the preload state?

A. Systolic peak
B. Beginning diastole
C. End diastolic pressure
D. The ventricular upstroke



Which one of the following statements about $ScvO_2$ is most correct?

A. $ScvO_2$ values <60% indicate vulnerable tissue oxygenation

B. $ScvO_2$ values >80% indicate adequate or increased tissue oxygenation

C. $ScvO_2$ values <60% indicate low oxygen consumption

D. $ScvO_2$ values >80% indicate increased oxygen consumption

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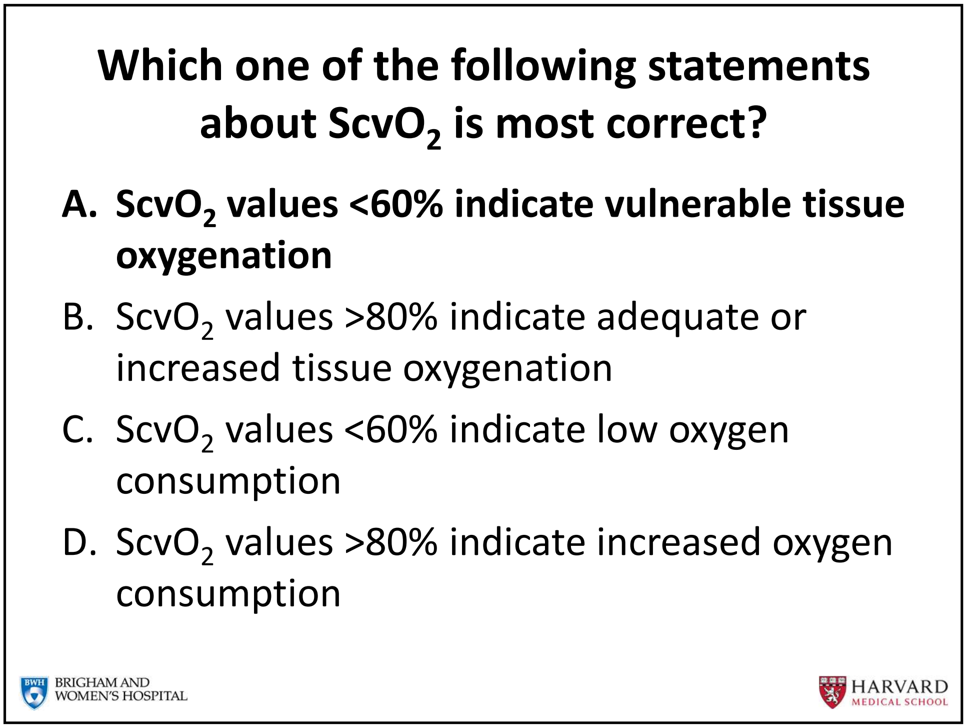
HARVARD MEDICAL SCHOOL



Which one of the following statements about $ScvO_2$ is most correct?

A. $ScvO_2$ values <60% indicate vulnerable tissue oxygenation

B. $ScvO_2$ values >80% indicate adequate or increased tissue oxygenation

C. $ScvO_2$ values <60% indicate low oxygen consumption

D. $ScvO_2$ values >80% indicate increased oxygen consumption

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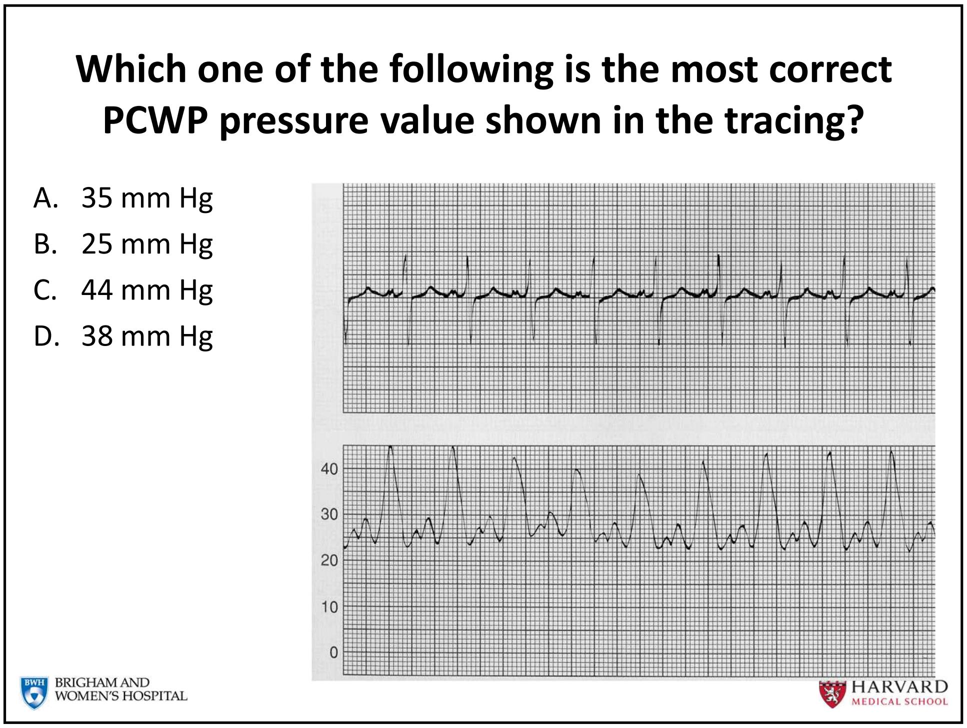

Which one of the following is the most correct PCWP pressure value shown in the tracing?

A. 35 mm Hg
B. 25 mm Hg
C. 44 mm Hg
D. 38 mm Hg

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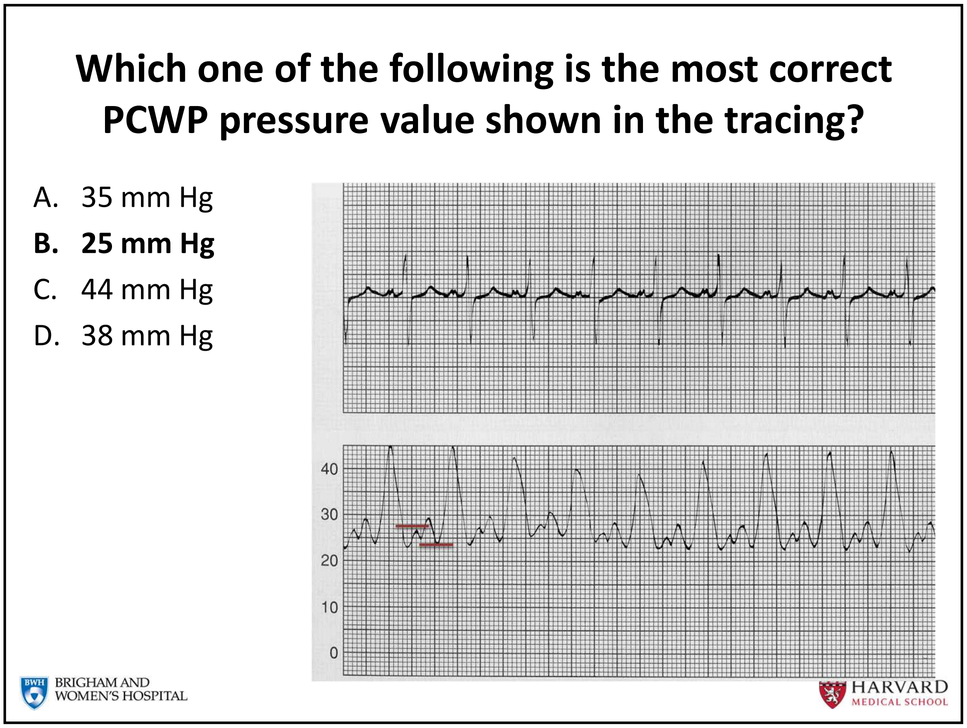

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HARVARD MEDICAL SCHOOL

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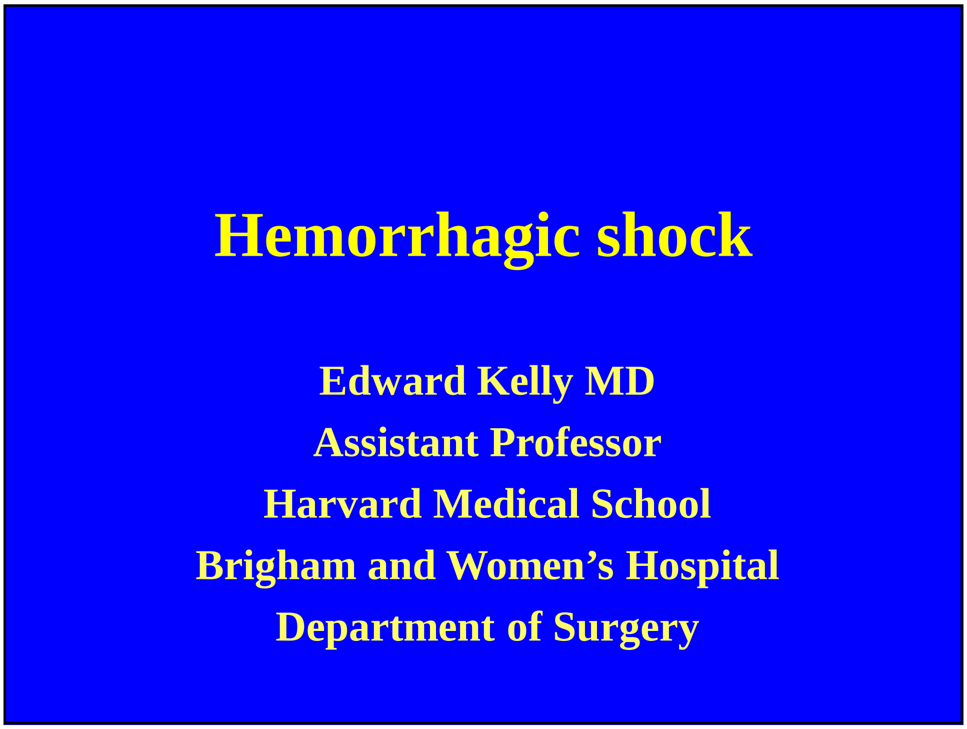
- The Pulmonary Artery Catheter Education Project (PACEP) http://www.pacep.org/ Collaborative project of the ACCP, ACCN, AANA, ASA, ATS, NHLBI, SCCM, and SCA



Hemorrhagic shock

Edward Kelly MD
Assistant Professor
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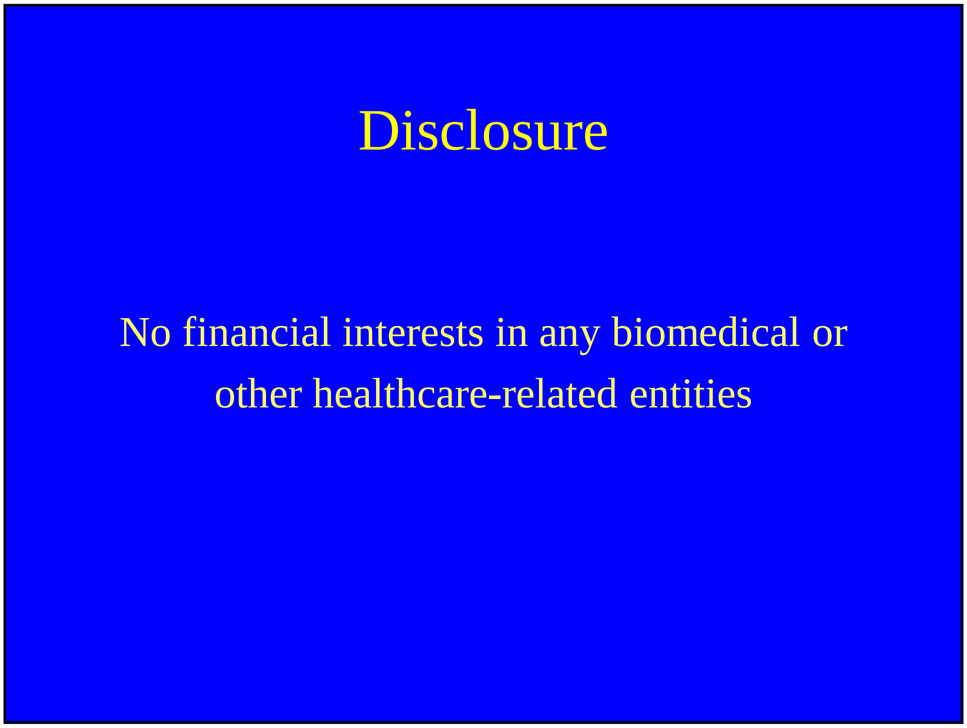
Department of Surgery



Disclosure

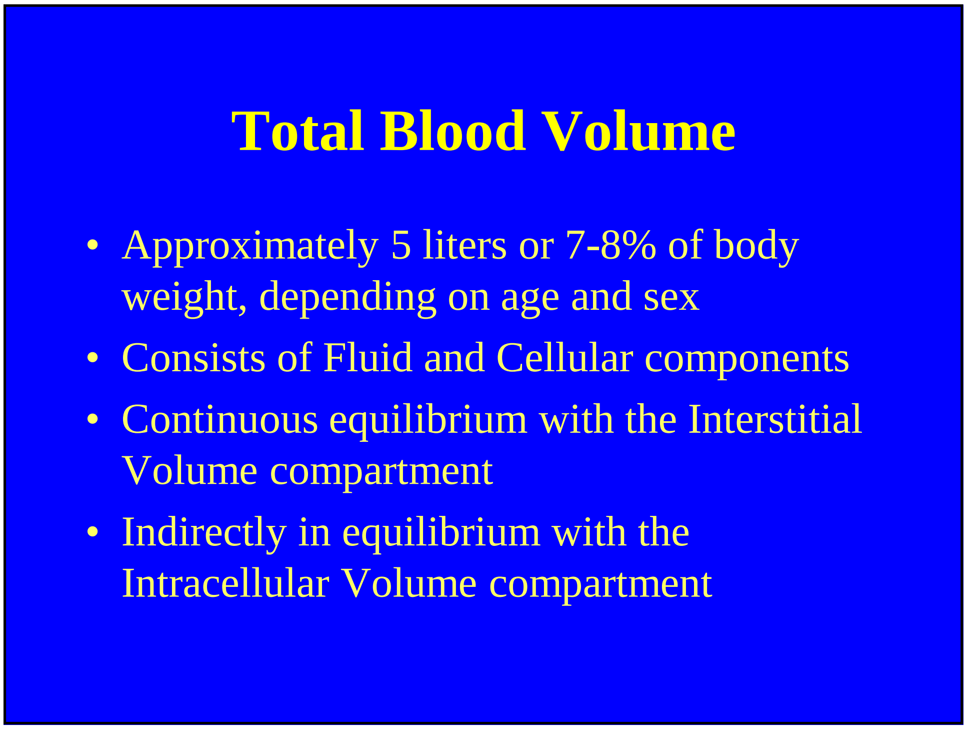
No financial interests in any biomedical or other healthcare-related entities

Overview

Normal Physiology Review
Shock Physiology
Decompensated Shock
Resuscitation ebb and flow

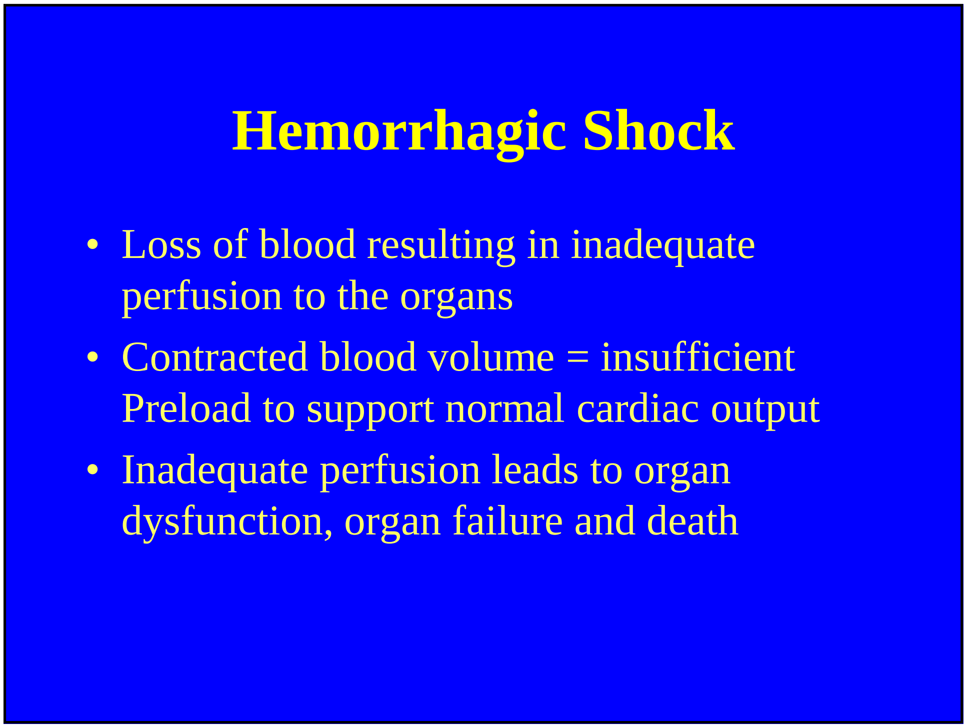
Normal Fluid Physiology

- For a 70 kg male:
  - 28 L Intracellular Fluid
  - 14 L Extracellular Fluid
    - 3 L Plasma (+ 2 L RBC volume = blood volume)
    - 11 L Interstial Fluid
      - Gel phase: Collagen and mucoproteins
      - Sol Phase: Small molecules



Total Blood Volume

- Approximately 5 liters or 7-8% of body weight, depending on age and sex
- Consists of Fluid and Cellular components
- Continuous equilibrium with the Interstitial Volume compartment
- Indirectly in equilibrium with the Intracellular Volume compartment



Hemorrhagic Shock

- Loss of blood resulting in inadequate perfusion to the organs
- Contracted blood volume = insufficient Preload to support normal cardiac output
- Inadequate perfusion leads to organ dysfunction, organ failure and death

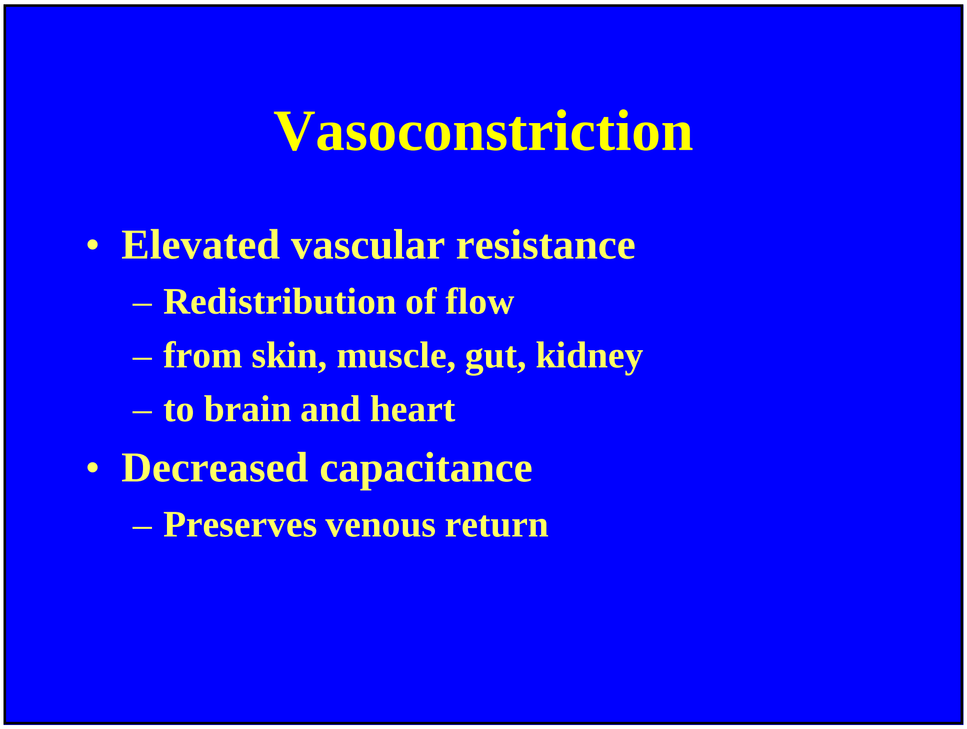
Hemorrhagic Shock

	Class I	Class II	Class III	Class IV
Blood loss	<750cc	750-1500	1500-2000	>2000
% BV	<15%	15-30%	30-40%	>40%
HR	<100	>100	>120	>140
BP	normal	normal	orthostatic	hypo
UOP	normal	normal	oliguric	anuric
LOC	anxious	agitated	confused	lethargy

Adapted from ATLS Manual 9th edition

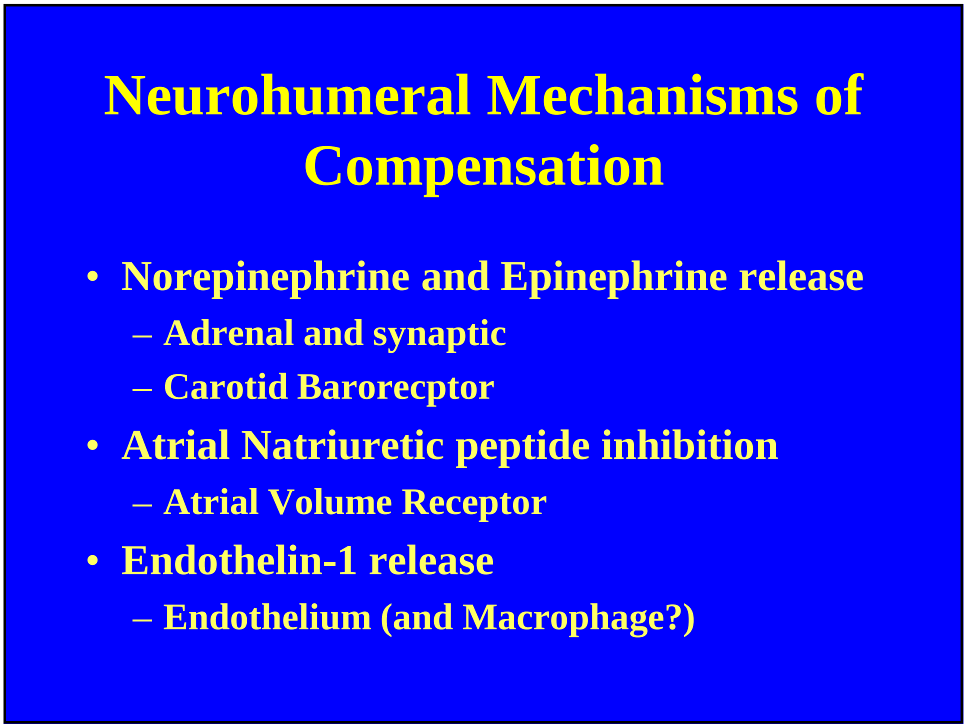
Compensation

- Class I and Class II Shock
- Vasoconstriction leads to redistribution of blood volume
  - maintain flow to vital organs (brain, heart)
  - maintain core temperature



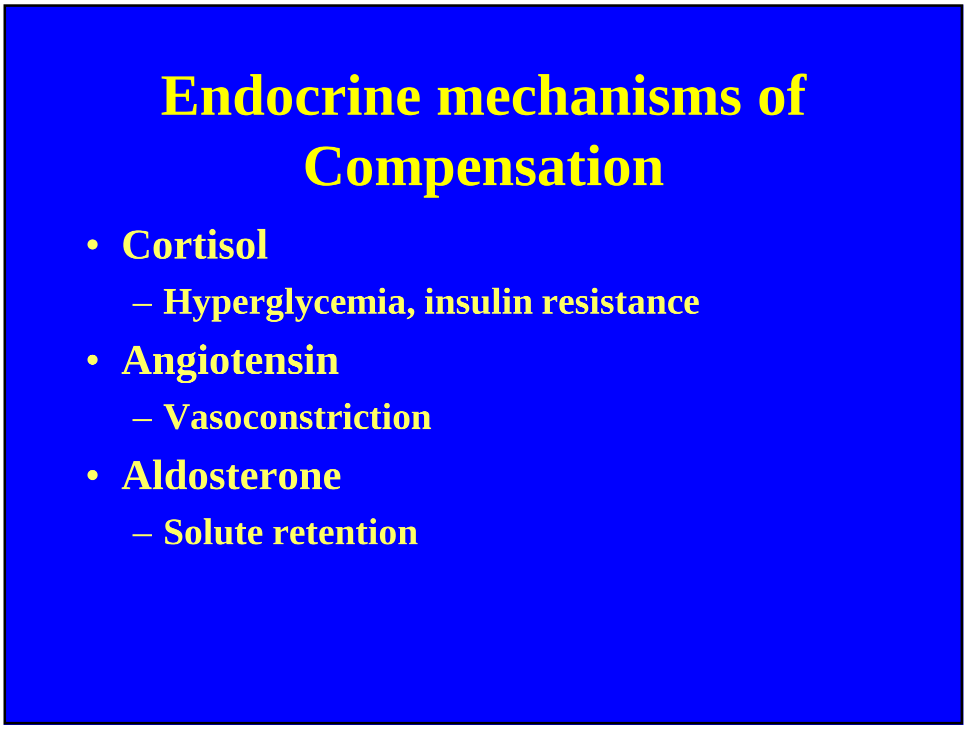
Vasoconstriction

- Elevated vascular resistance
  - Redistribution of flow
  - from skin, muscle, gut, kidney
  - to brain and heart
- Decreased capacitance
  - Preserves venous return



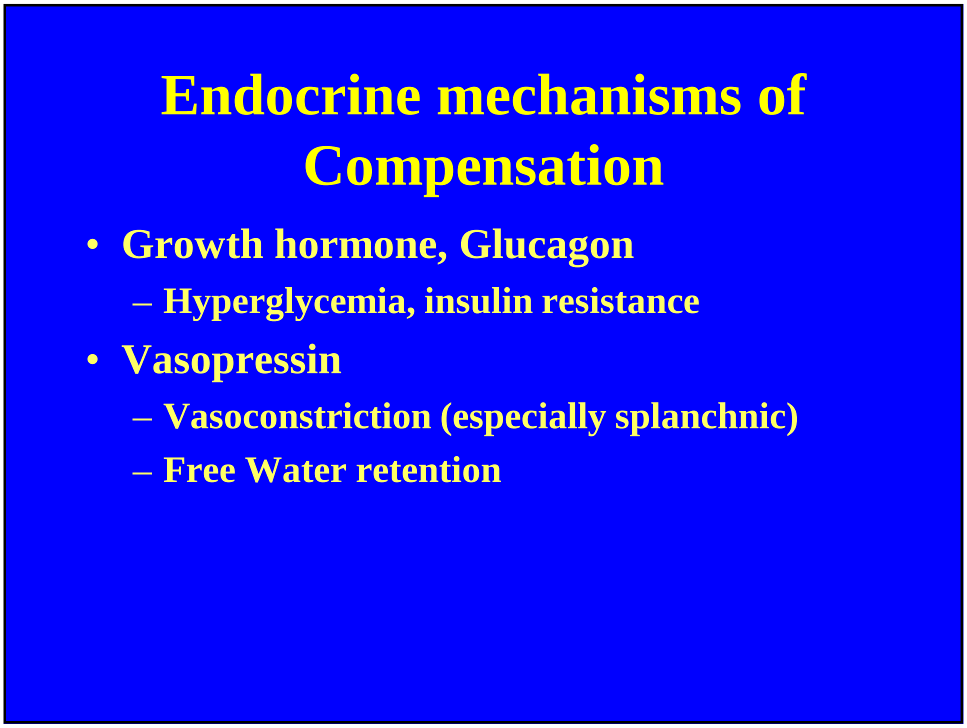
Neurohumeral Mechanisms of Compensation

- Norepinephrine and Epinephrine release
  - Adrenal and synaptic
  - Carotid Barorecptor
- Atrial Natriuretic peptide inhibition
  - Atrial Volume Receptor
- Endothelin-1 release
  - Endothelium (and Macrophage?)



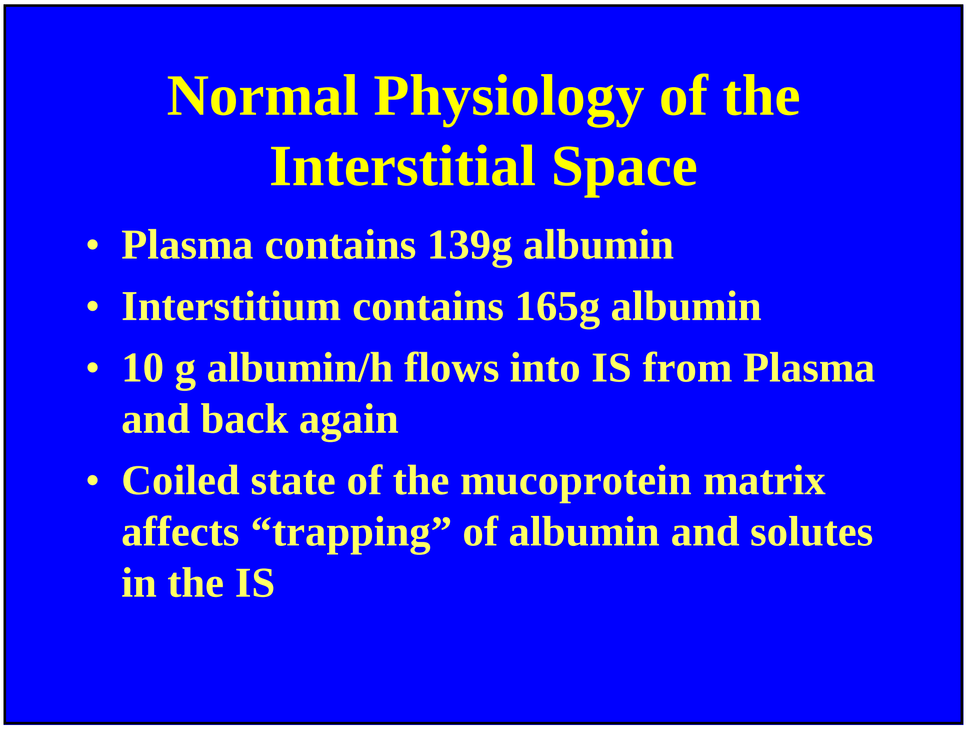
Endocrine mechanisms of Compensation

- Cortisol
  - Hyperglycemia, insulin resistance
- Angiotensin
  - Vasoconstriction
- Aldosterone
  - Solute retention



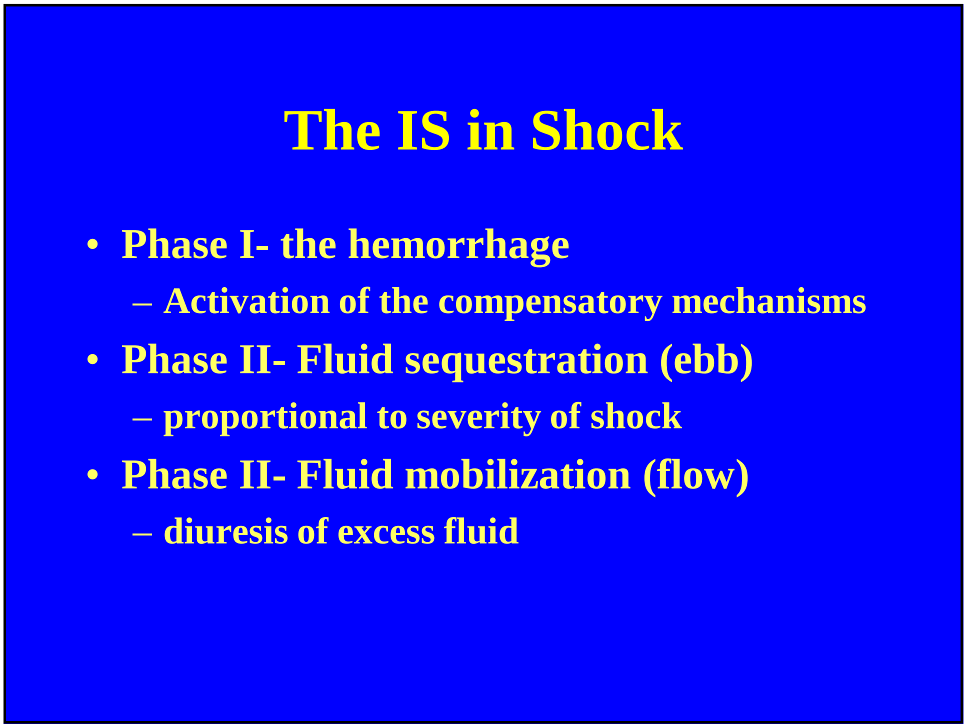
Endocrine mechanisms of Compensation

- Growth hormone, Glucagon
  - Hyperglycemia, insulin resistance
- Vasopressin
  - Vasoconstriction (especially splanchnic)
  - Free Water retention



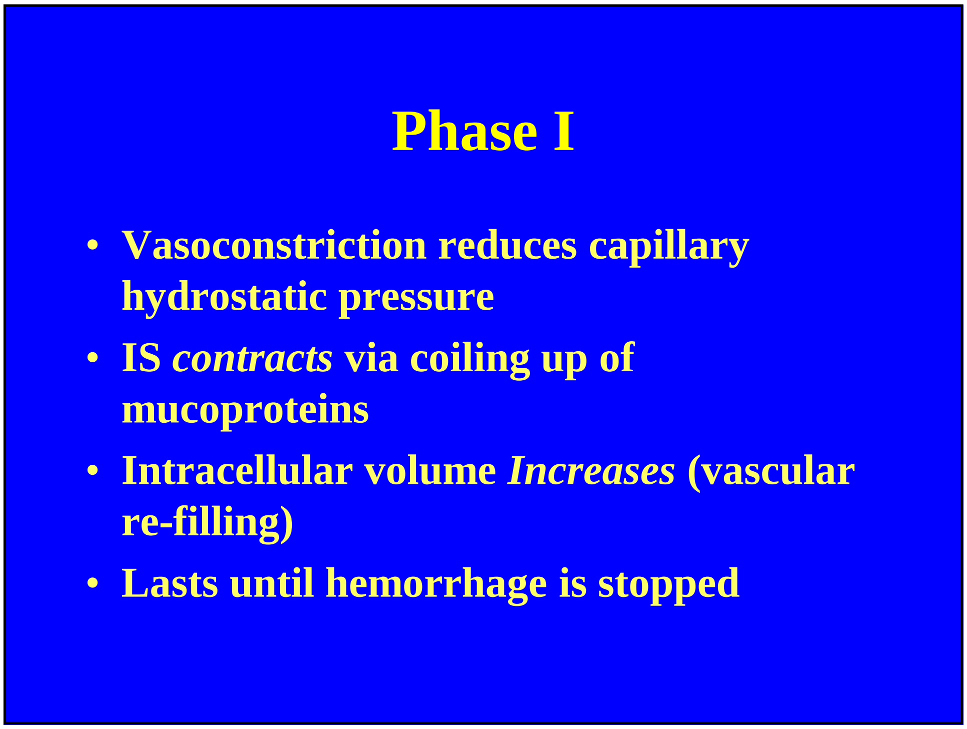
Normal Physiology of the Interstitial Space

- Plasma contains 139g albumin
- Interstitium contains 165g albumin
- 10 g albumin/h flows into IS from Plasma and back again
- Coiled state of the mucoprotein matrix affects “trapping” of albumin and solutes in the IS



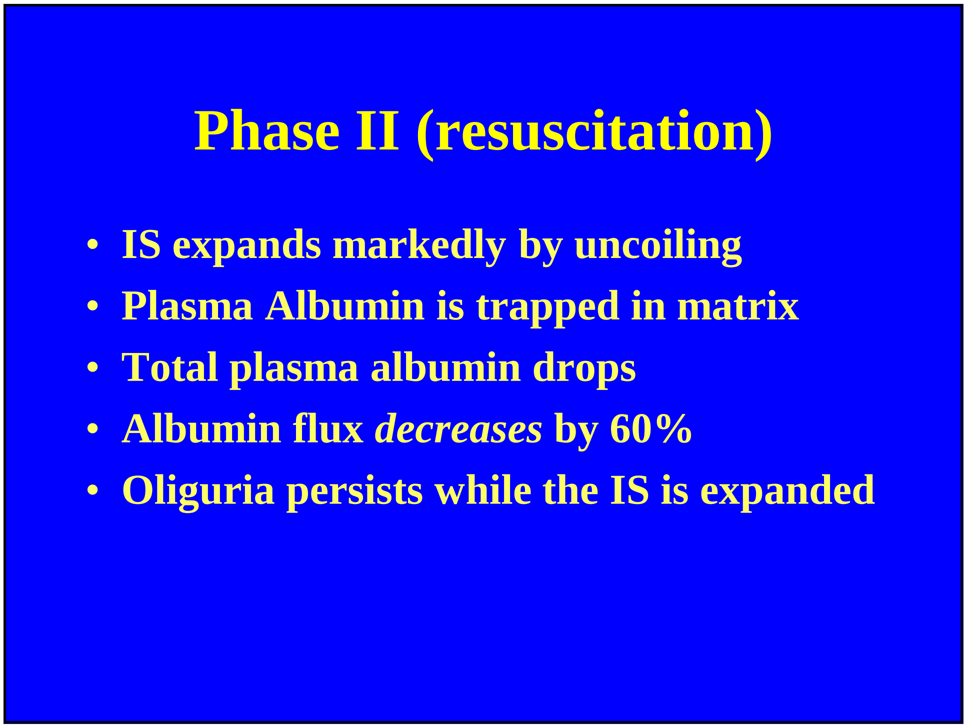
The IS in Shock

- Phase I- the hemorrhage
  - Activation of the compensatory mechanisms
- Phase II- Fluid sequestration (ebb)
  - proportional to severity of shock
- Phase II- Fluid mobilization (flow)
  - diuresis of excess fluid



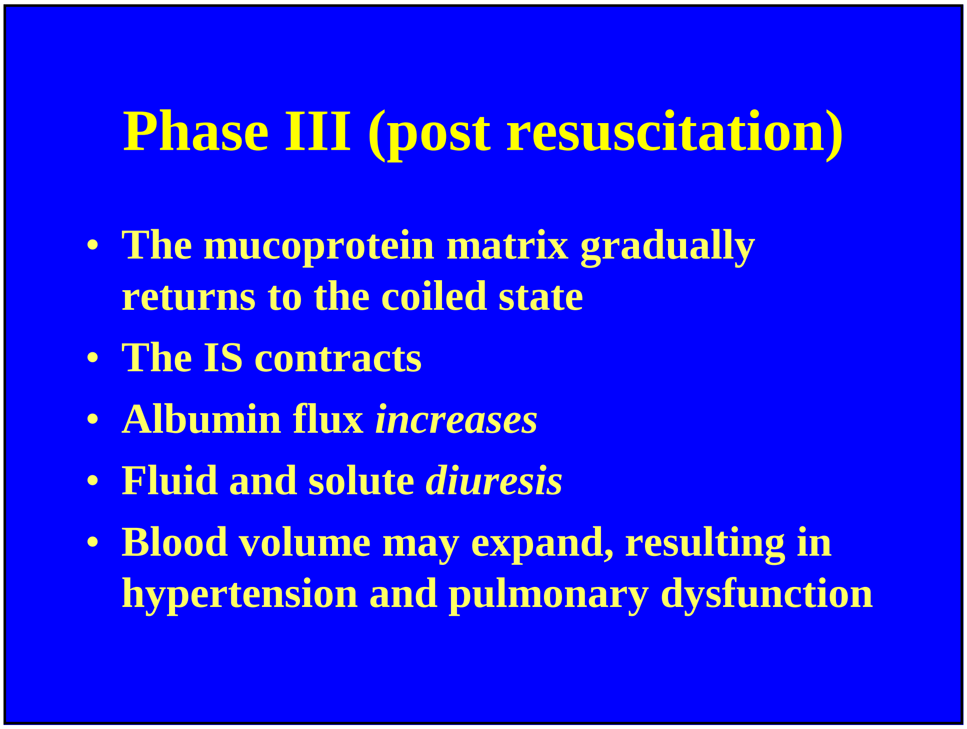
Phase I

- Vasoconstriction reduces capillary hydrostatic pressure
- IS *contracts* via coiling up of mucoproteins
- Intracellular volume *Increases* (vascular re-filling)
- Lasts until hemorrhage is stopped



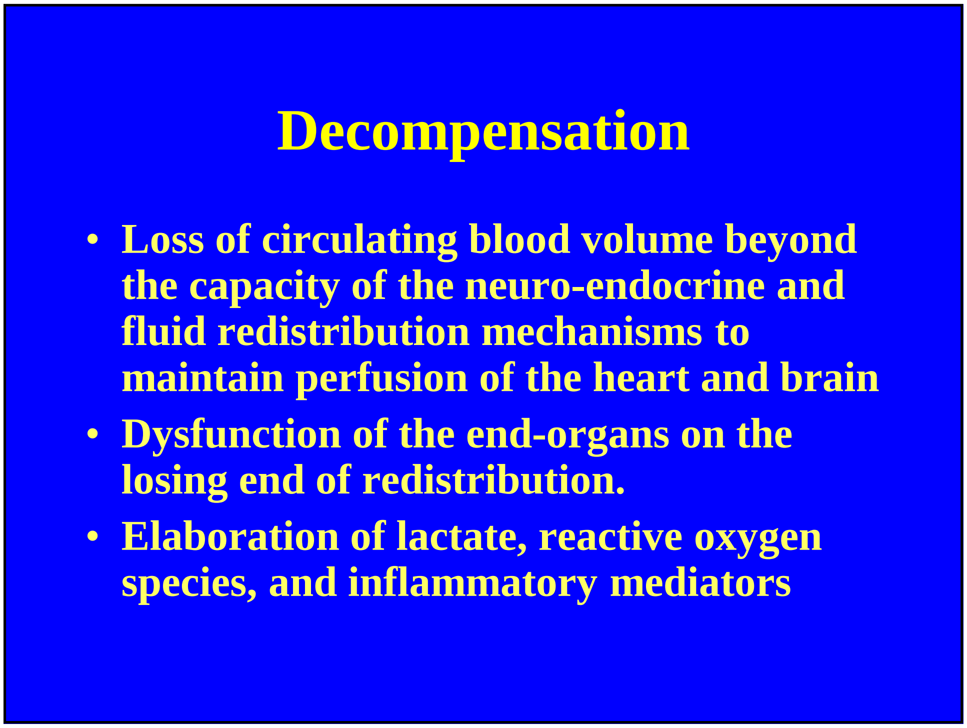
Phase II (resuscitation)

- IS expands markedly by uncoiling
- Plasma Albumin is trapped in matrix
- Total plasma albumin drops
- Albumin flux *decreases* by 60%
- Oliguria persists while the IS is expanded



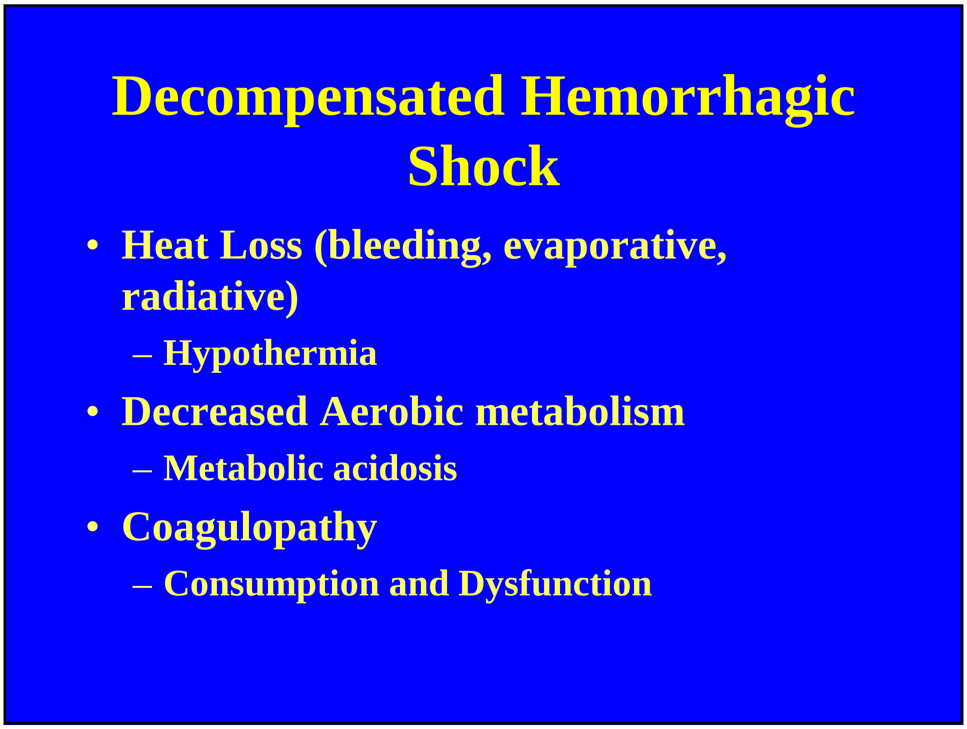
Phase III (post resuscitation)

- The mucoprotein matrix gradually returns to the coiled state
- The IS contracts
- Albumin flux *increases*
- Fluid and solute *diuresis*
- Blood volume may expand, resulting in hypertension and pulmonary dysfunction



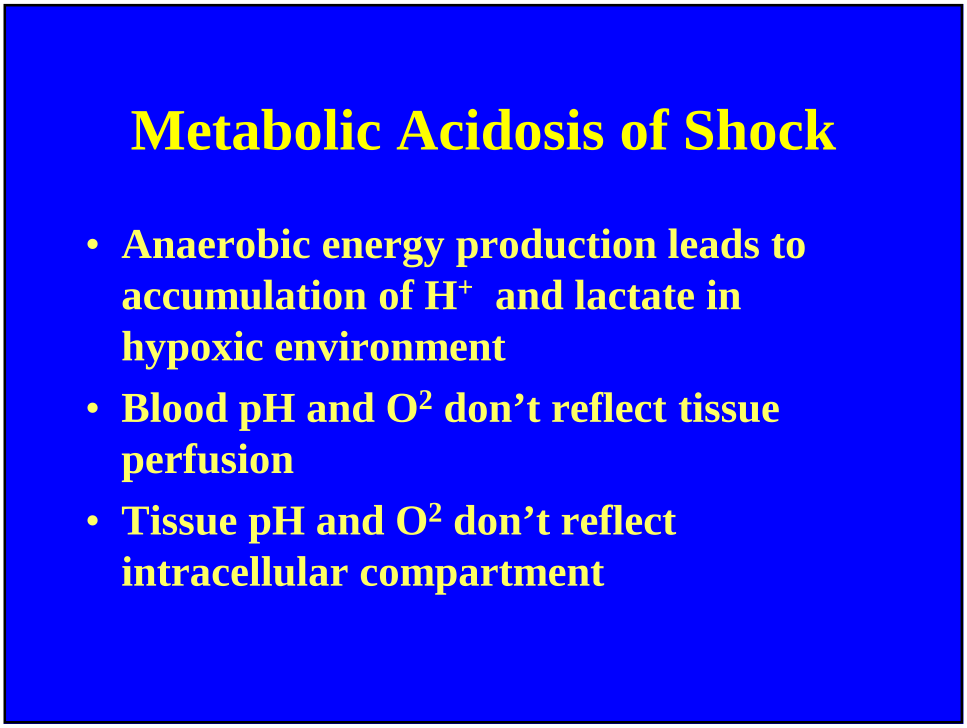
Decompensation

- Loss of circulating blood volume beyond the capacity of the neuro-endocrine and fluid redistribution mechanisms to maintain perfusion of the heart and brain
- Dysfunction of the end-organs on the losing end of redistribution.
- Elaboration of lactate, reactive oxygen species, and inflammatory mediators



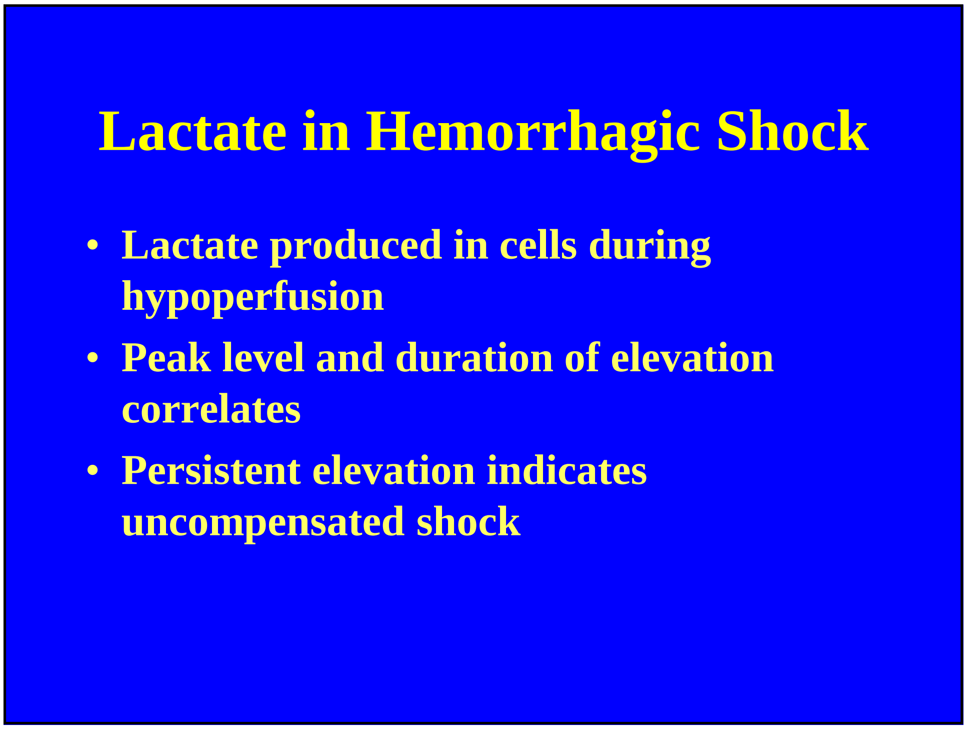
Decompensated Hemorrhagic Shock

- Heat Loss (bleeding, evaporative, radiative)
  - Hypothermia
- Decreased Aerobic metabolism
  - Metabolic acidosis
- Coagulopathy
  - Consumption and Dysfunction



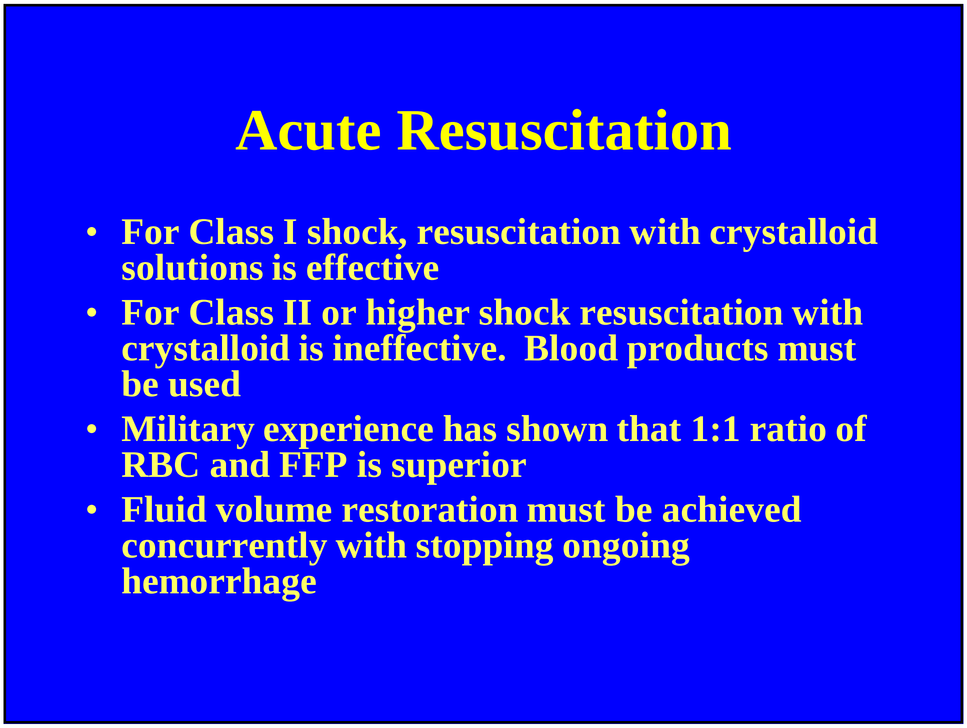
Metabolic Acidosis of Shock

- Anaerobic energy production leads to accumulation of H^+ and lactate in hypoxic environment
- Blood pH and O^2 don’t reflect tissue perfusion
- Tissue pH and O^2 don’t reflect intracellular compartment



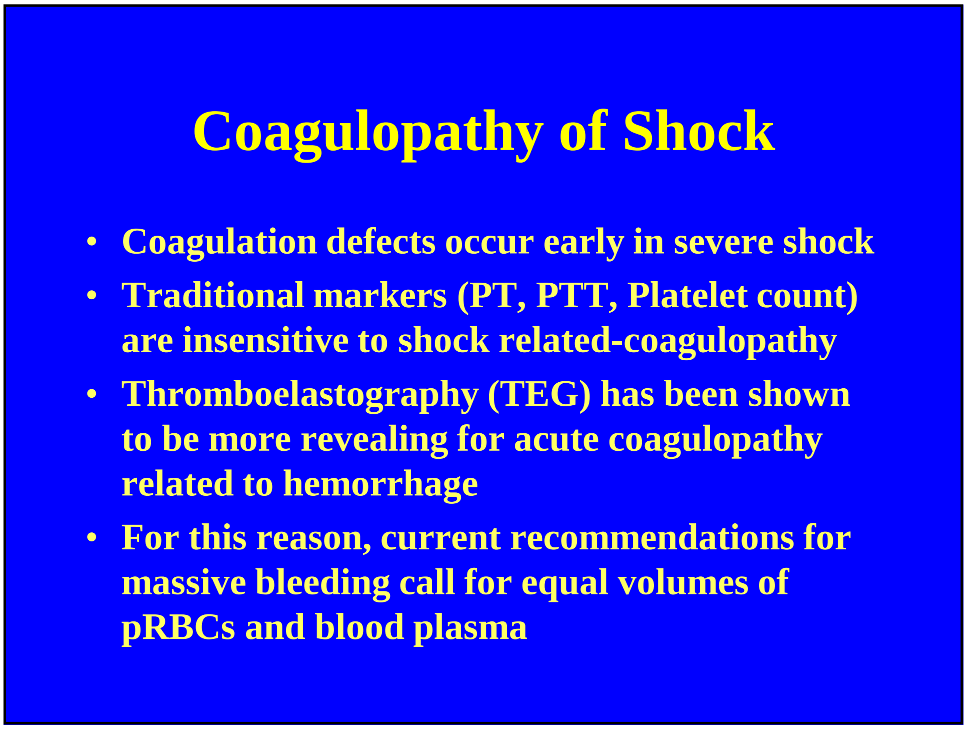
Lactate in Hemorrhagic Shock

- Lactate produced in cells during hypoperfusion
- Peak level and duration of elevation correlates
- Persistent elevation indicates uncompensated shock



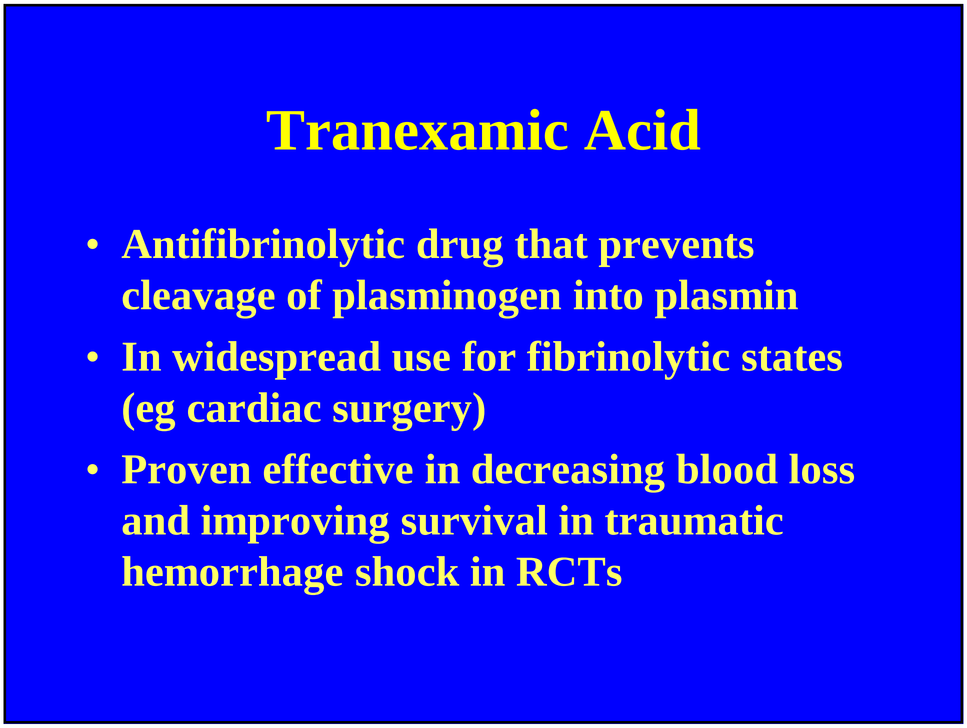
Acute Resuscitation

- For Class I shock, resuscitation with crystalloid solutions is effective
- For Class II or higher shock resuscitation with crystalloid is ineffective. Blood products must be used
- Military experience has shown that 1:1 ratio of RBC and FFP is superior
- Fluid volume restoration must be achieved concurrently with stopping ongoing hemorrhage



Coagulopathy of Shock

- Coagulation defects occur early in severe shock
- Traditional markers (PT, PTT, Platelet count) are insensitive to shock related-coagulopathy
- Thromboelastography (TEG) has been shown to be more revealing for acute coagulopathy related to hemorrhage
- For this reason, current recommendations for massive bleeding call for equal volumes of pRBCs and blood plasma



Tranexamic Acid

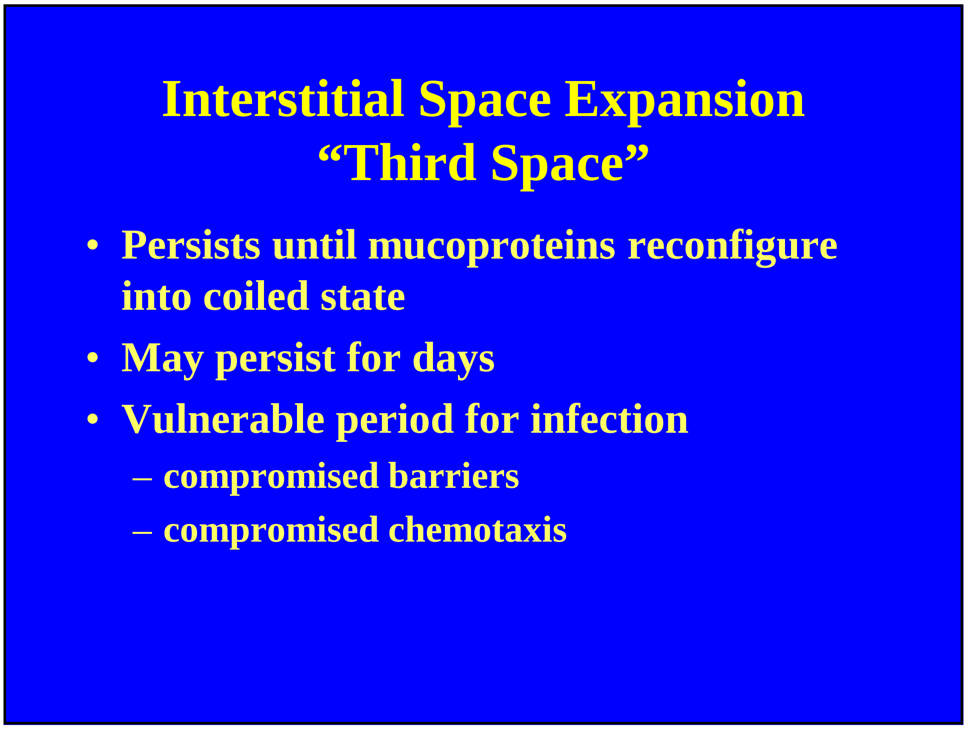
- Antifibrinolytic drug that prevents cleavage of plasminogen into plasmin
- In widespread use for fibrinolytic states (eg cardiac surgery)
- Proven effective in decreasing blood loss and improving survival in traumatic hemorrhage shock in RCTs

Acute Resuscitation- Access

- 2 Large Bore peripheral IV lines preferred
- 8 French central line
- Unacceptable:
  - Peripheral IV smaller than 18 ga
  - Triple lumen CVL
  - PICC

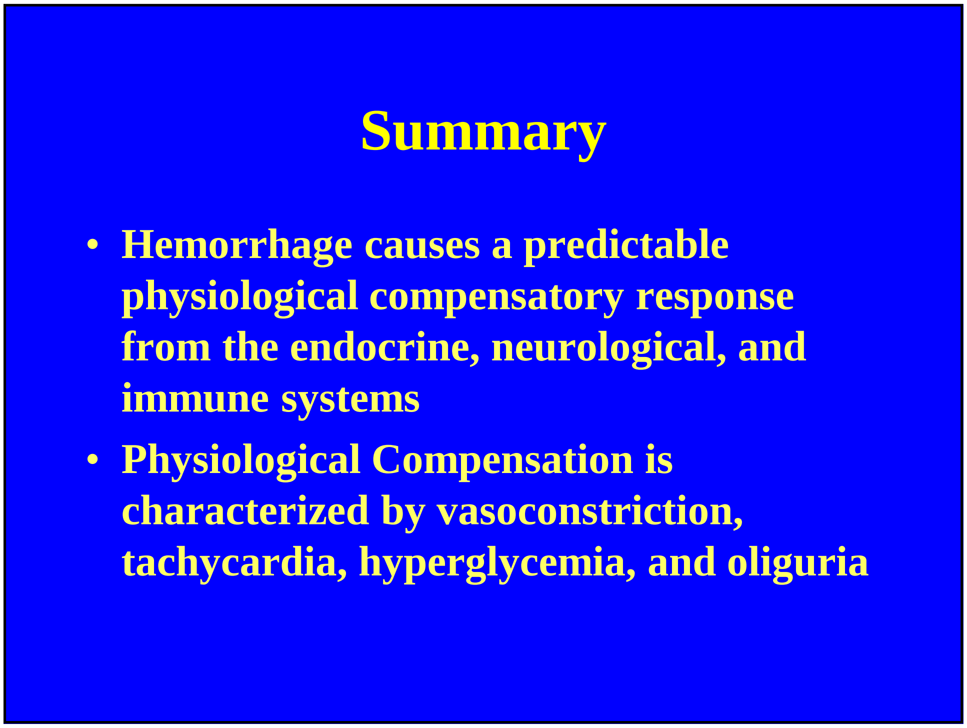
Interstitial Space Expansion "Third Space"

- Coincides with tissue acidosis and free radical formation
- Results from mucoprotein uncoiling
- Increases ability of tissue to tolerate acidosis
  - Protein buffer
  - Expanded volume



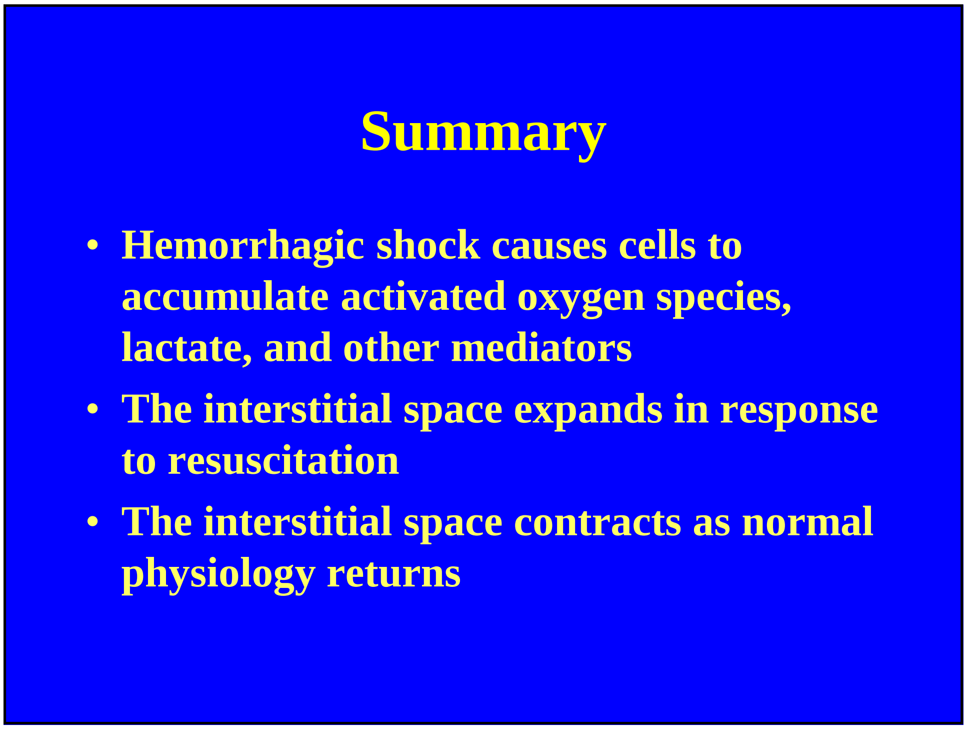
Interstitial Space Expansion “Third Space”

- Persists until mucoproteins reconfigure into coiled state
- May persist for days
- Vulnerable period for infection
  - compromised barriers
  - compromised chemotaxis



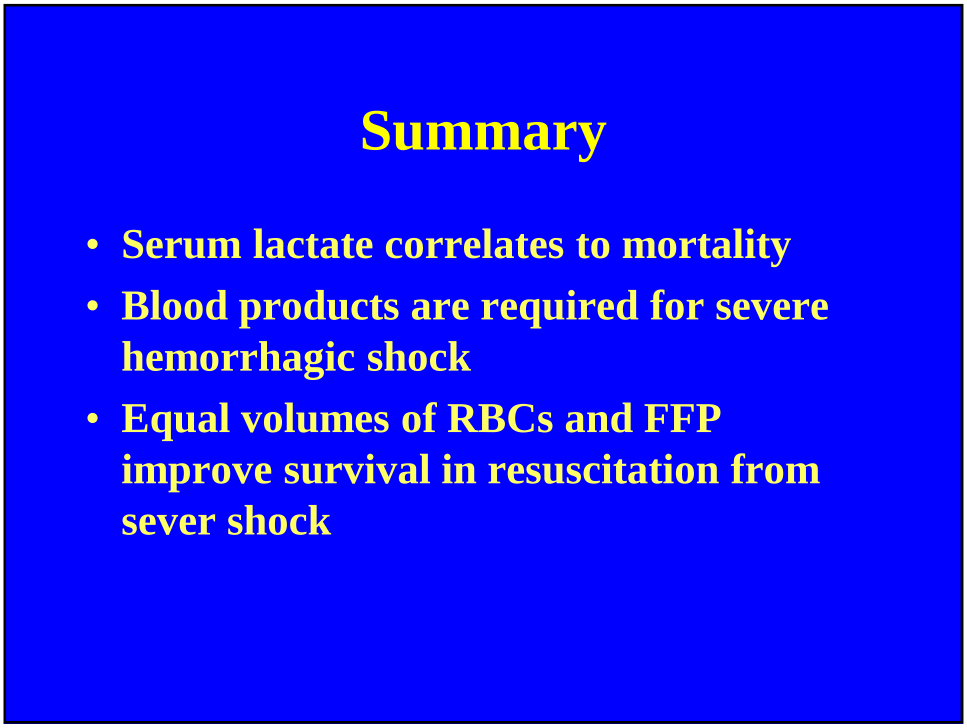
Summary

- Hemorrhage causes a predictable physiological compensatory response from the endocrine, neurological, and immune systems
- Physiological Compensation is characterized by vasoconstriction, tachycardia, hyperglycemia, and oliguria



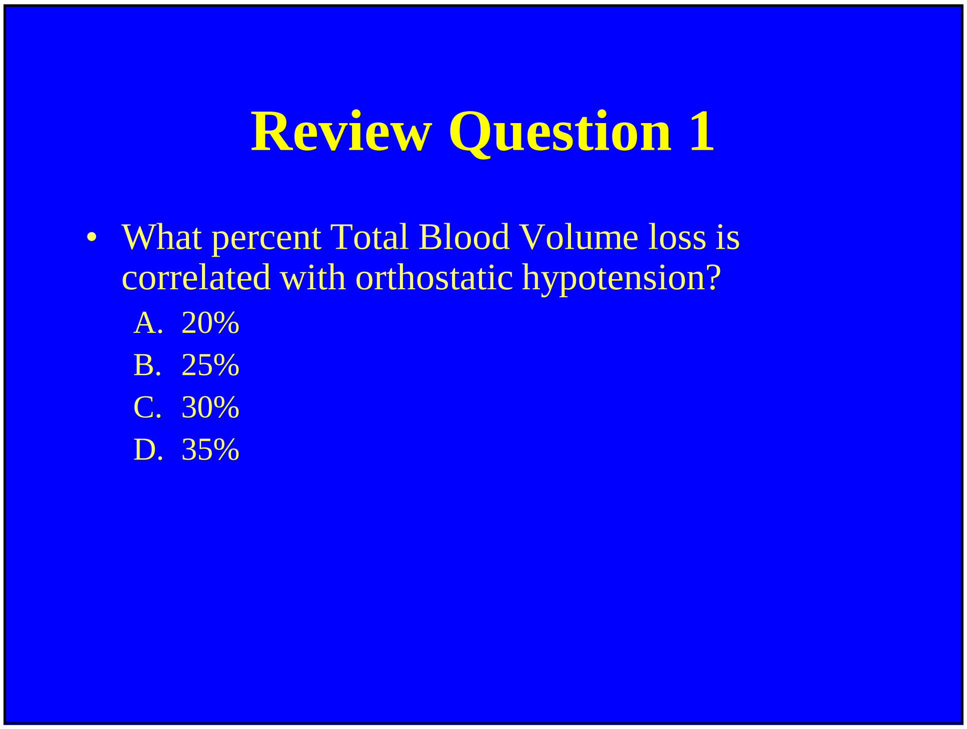
Summary

- Hemorrhagic shock causes cells to accumulate activated oxygen species, lactate, and other mediators
- The interstitial space expands in response to resuscitation
- The interstitial space contracts as normal physiology returns



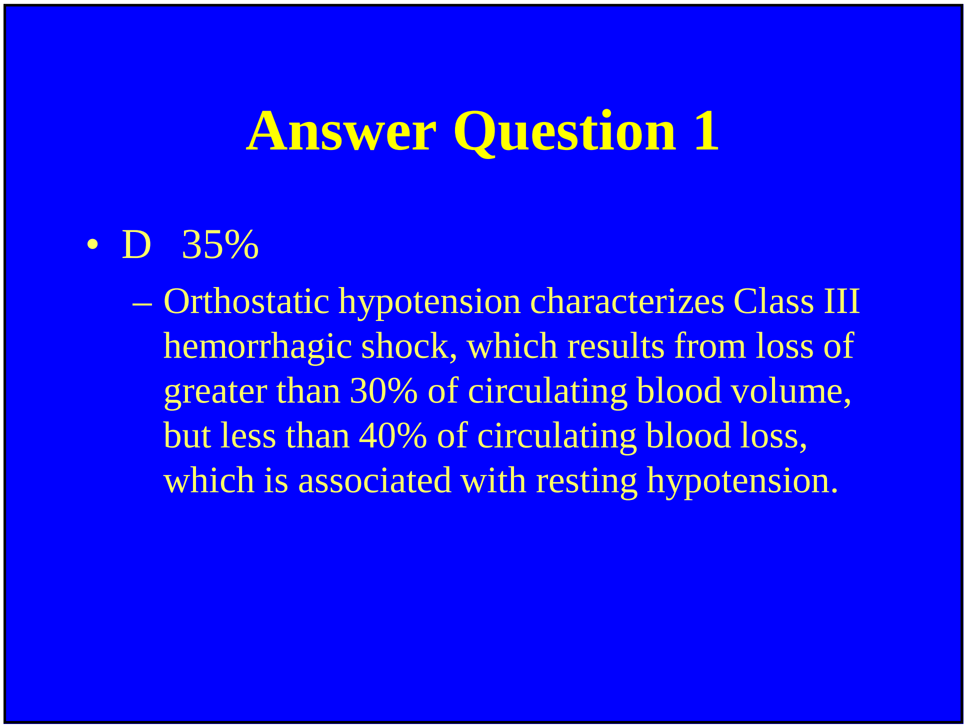
Summary

- Serum lactate correlates to mortality
- Blood products are required for severe hemorrhagic shock
- Equal volumes of RBCs and FFP improve survival in resuscitation from sever shock



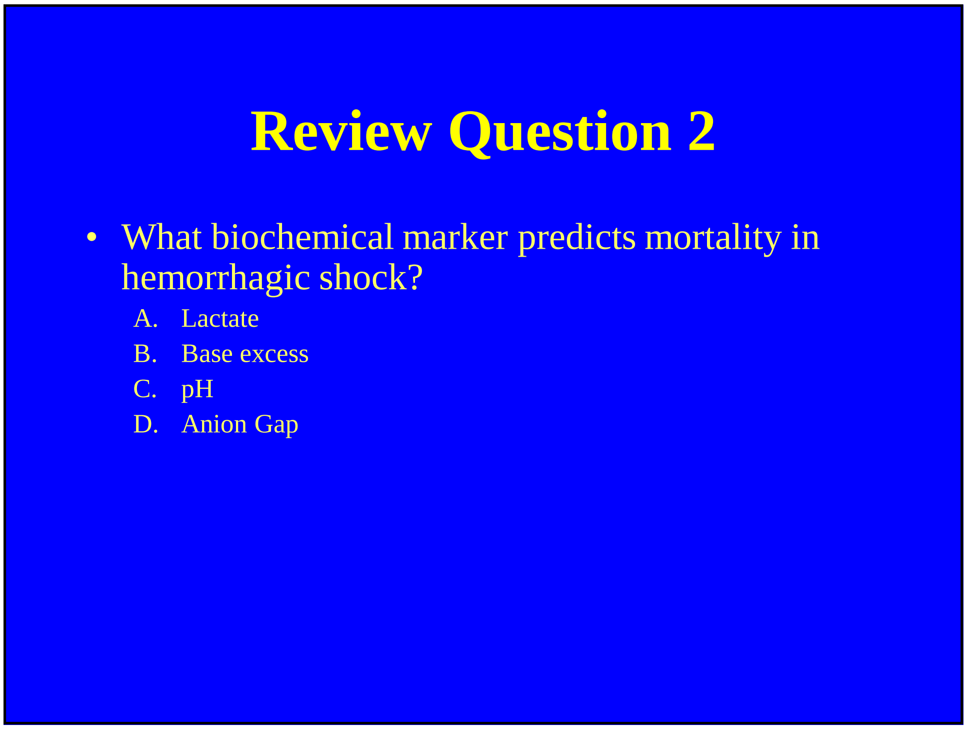
Review Question 1

- What percent Total Blood Volume loss is correlated with orthostatic hypotension?
  - A. 20%
  - B. 25%
  - C. 30%
  - D. 35%



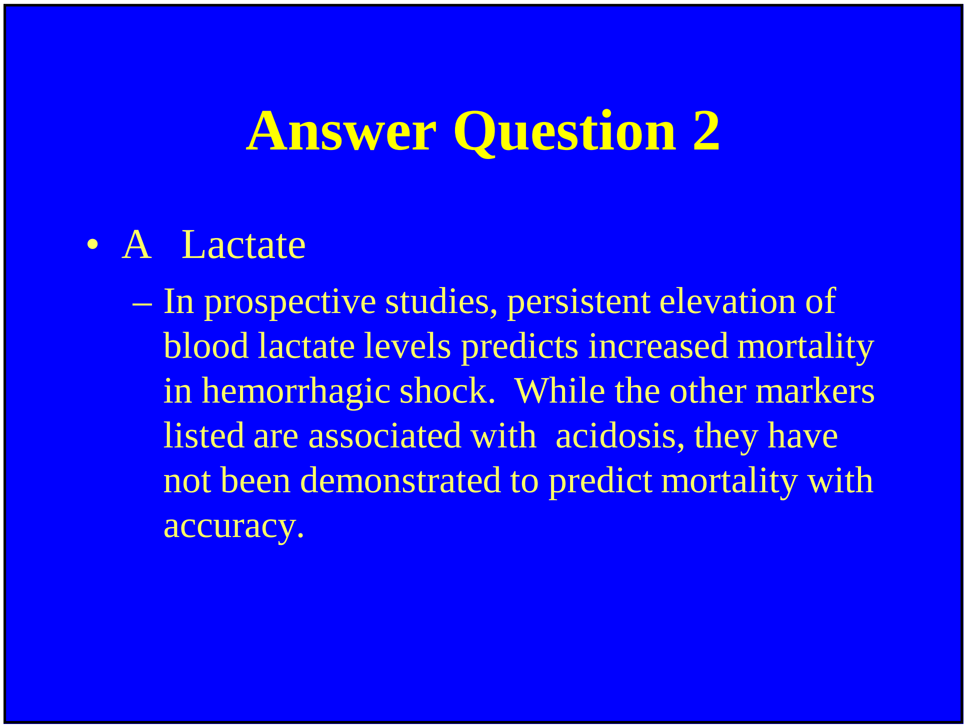
Answer Question 1

- D 35%
  - – Orthostatic hypotension characterizes Class III hemorrhagic shock, which results from loss of greater than 30% of circulating blood volume, but less than 40% of circulating blood loss, which is associated with resting hypotension.



Review Question 2

- What biochemical marker predicts mortality in hemorrhagic shock?
  - A. Lactate
  - B. Base excess
  - C. pH
  - D. Anion Gap



Answer Question 2

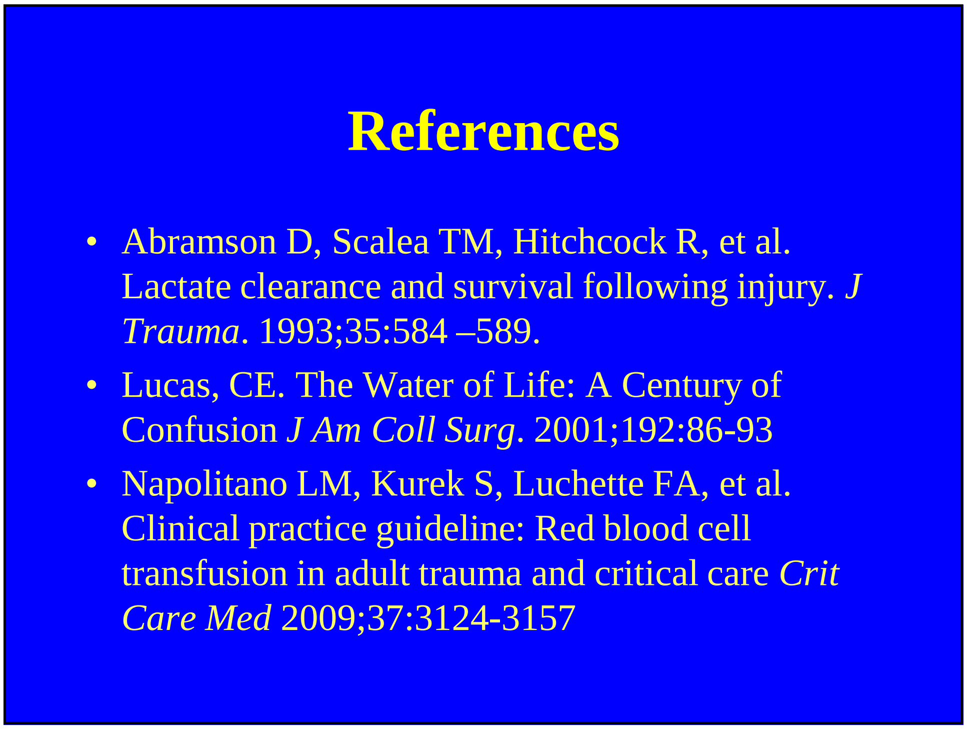
- A Lactate
  - In prospective studies, persistent elevation of blood lactate levels predicts increased mortality in hemorrhagic shock. While the other markers listed are associated with acidosis, they have not been demonstrated to predict mortality with accuracy.

Review Question 3

- What is the earliest laboratory marker of hemorrhage related coagulopathy?
  A. Fibrinogen
  B. Thromboelastography
  C. Platelet count
  D. D-dimer

Answer Question 3

- B Thromboelastography
  - TEG has been show to reveal abnormal clotting in early hemorrhagic shock, before the other markers.



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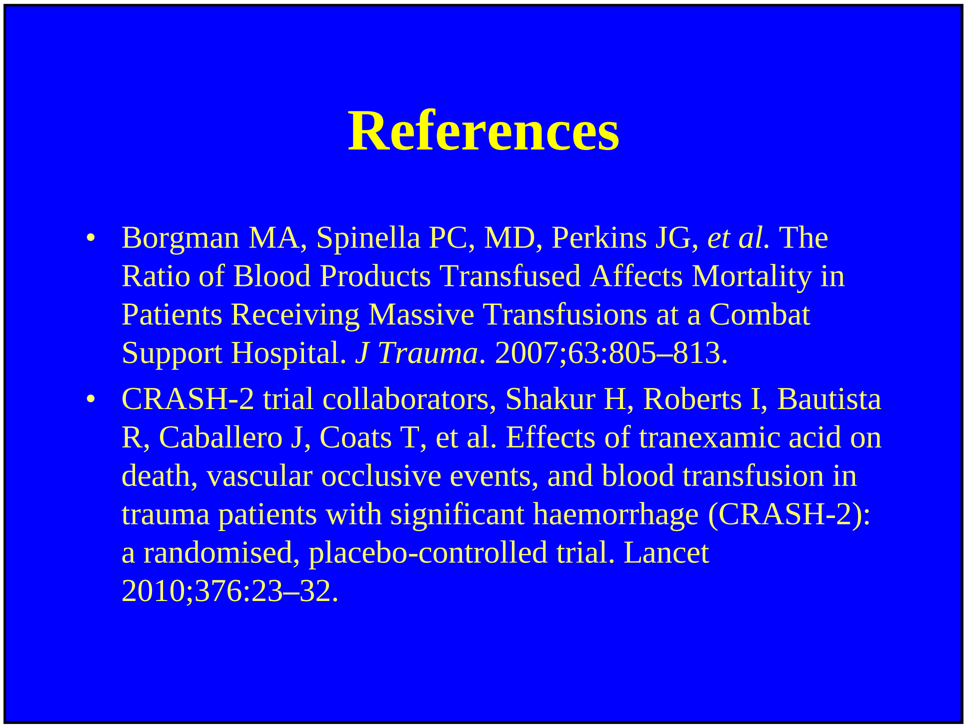

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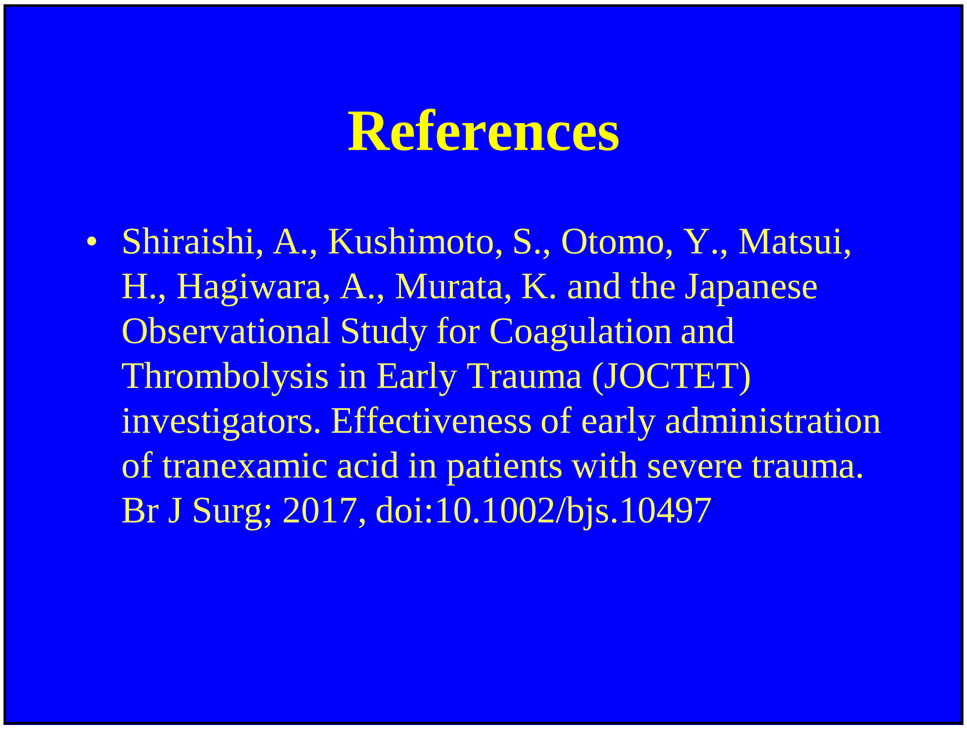

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Approach to Diagnosis and Management of Cardiogenic Shock

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Cardiovascular Division
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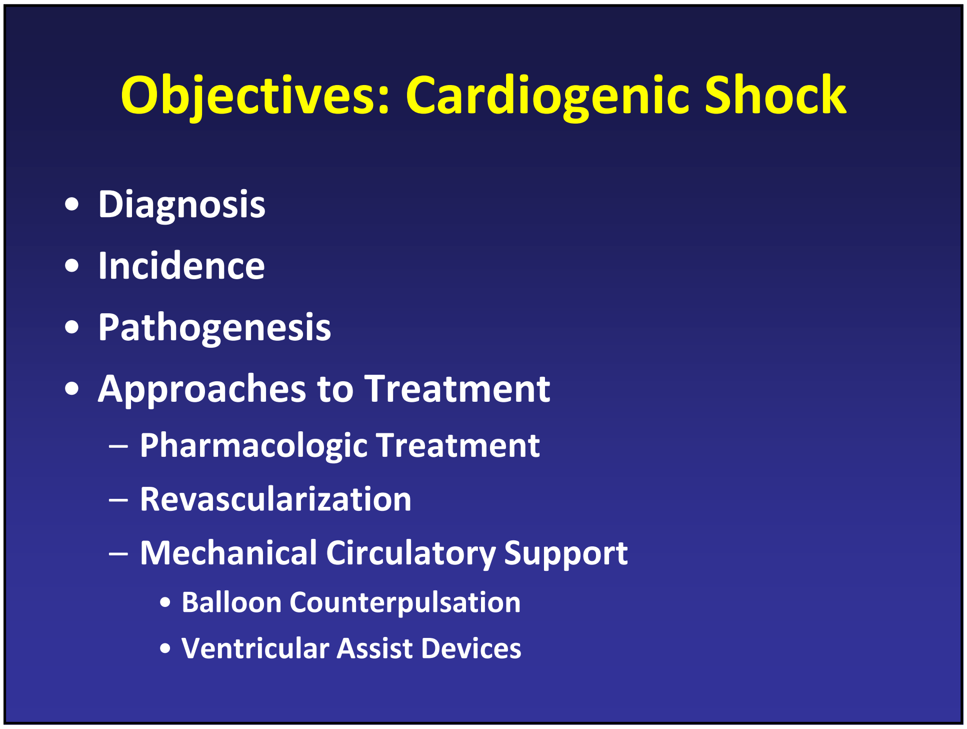
Disclosures

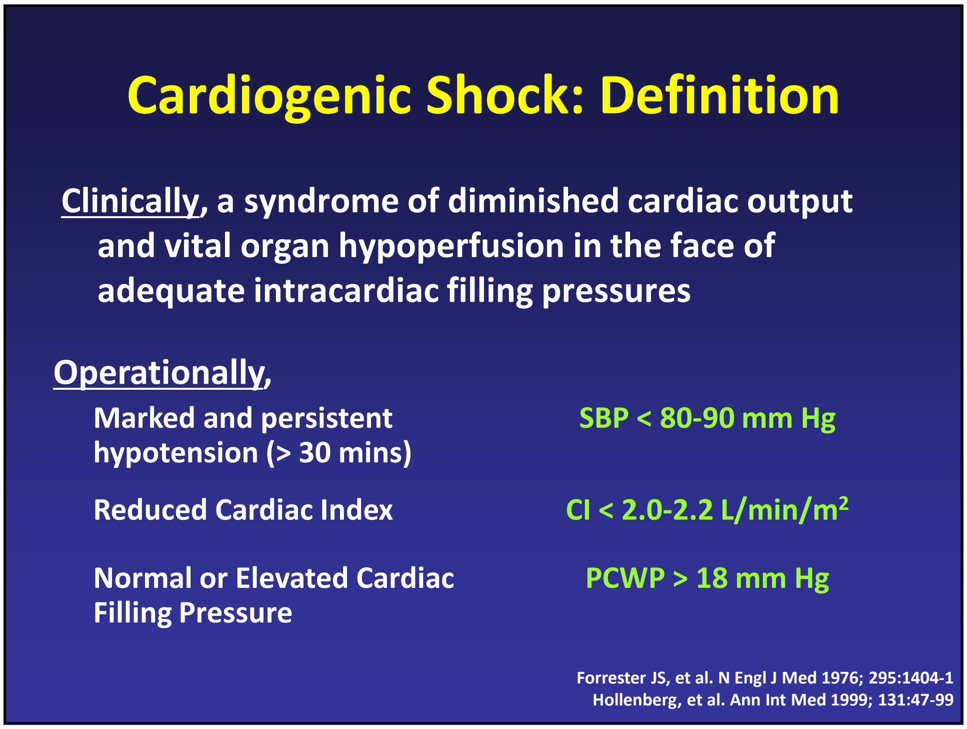
Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

- Consulting
  - Novartis, Relypsa, St. Jude Medical/Abbott, Janssen, Sanofi, AstraZeneca
- Research Grants
  - Novartis



Objectives: Cardiogenic Shock

- Diagnosis
- Incidence
- Pathogenesis
- Approaches to Treatment
  - Pharmacologic Treatment
  - Revascularization
  - Mechanical Circulatory Support
    - Balloon Counterpulsation
    - Ventricular Assist Devices



Cardiogenic Shock: Definition

Clinically, a syndrome of diminished cardiac output and vital organ hypoperfusion in the face of adequate intracardiac filling pressures

Operationally,

Marked and persistent hypotension (> 30 mins)	SBP < 80-90 mm Hg
Reduced Cardiac Index	CI < 2.0-2.2 L/min/m^2
Normal or Elevated Cardiac Filling Pressure	PCWP > 18 mm Hg

Forrester JS, et al. N Engl J Med 1976; 295:1404-1
Hollenberg, et al. Ann Int Med 1999; 131:47-99

Causes of Cardiogenic Shock

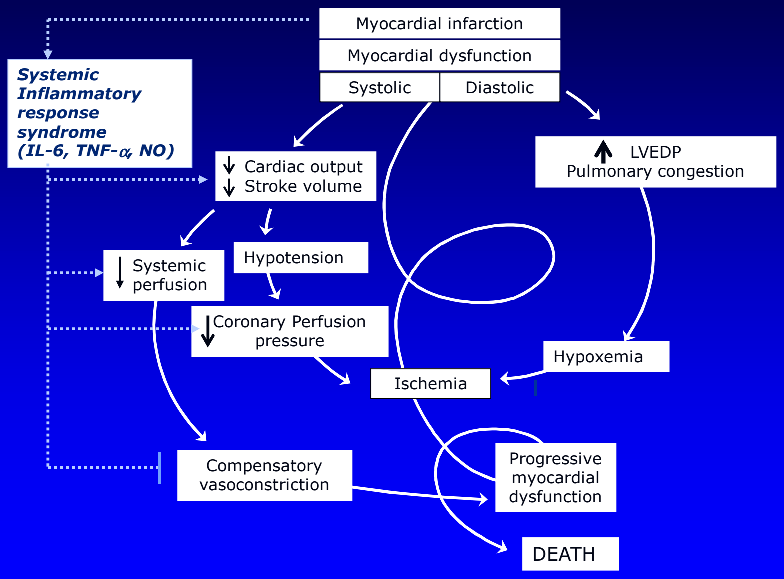
Acute MI

- **Pump Failure**
  - Large infarction
  - Smaller infarctions with preexisting CHF
  - Infarction extension or expansion
- **Mechanical complications**
  - VSD
  - Acute MR
  - Free Wall rupture
- **RV infarction**

Non-coronary causes

- **Fulminant Myocarditis**
- **Acute valvular insufficiency (e.g. endocarditis, trauma, chordal rupture)**
- **Obstruction to LV outflow (e.g. aortic stenosis, HCM)**
- **Obstruction to LV inflow (e.g. myxoma, MS)**
- **Aortic Dissection**
- **Pericardial Tamponade**
- **Massive pulmonary embolism**
- **End-Stage Cardiomyopathy**
- **Prolonged Cardiopulmonary Bypass**
- **Cardiac Contusion**

Pathophysiology of Cardiogenic Shock



Myocardial infarction

Myocardial dysfunction

Systolic | Diastolic

Systemic Inflammatory response syndrome (IL-6, TNF-α, NO)

↓ Cardiac output
↓ Stroke volume

↑ LVEDP
Pulmonary congestion

↓ Systemic perfusion

Hypotension

↓ Coronary Perfusion pressure

Hypoxemia

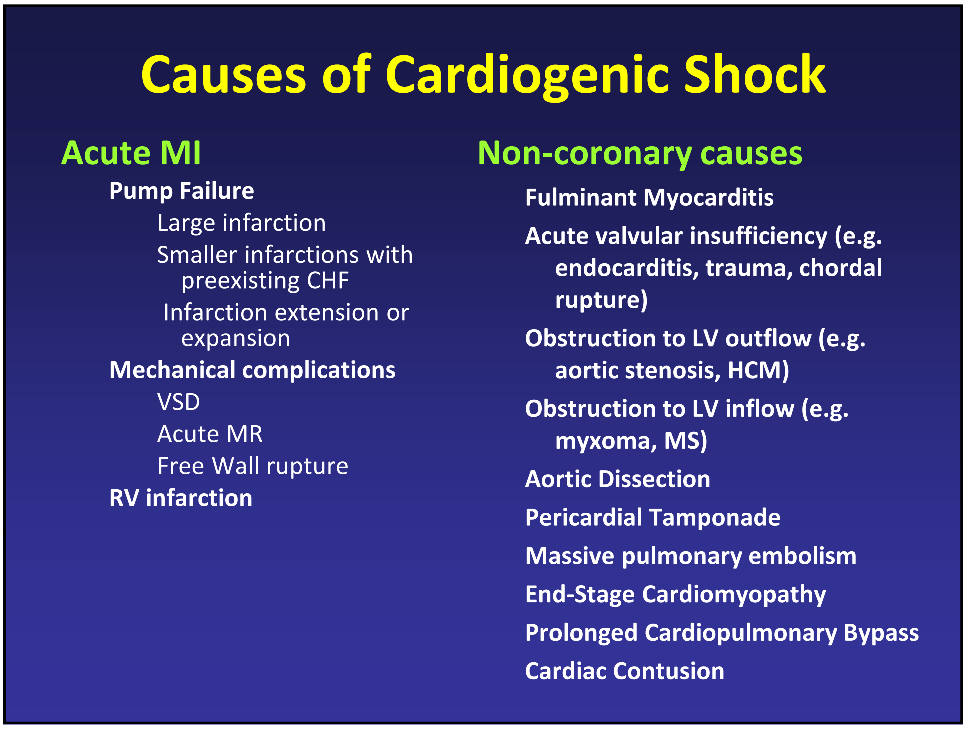
Ischemia

Compensatory vasoconstriction

Progressive myocardial dysfunction

DEATH

Reynolds HR, Hochman JS Circulation 2008; 117: 686-97.



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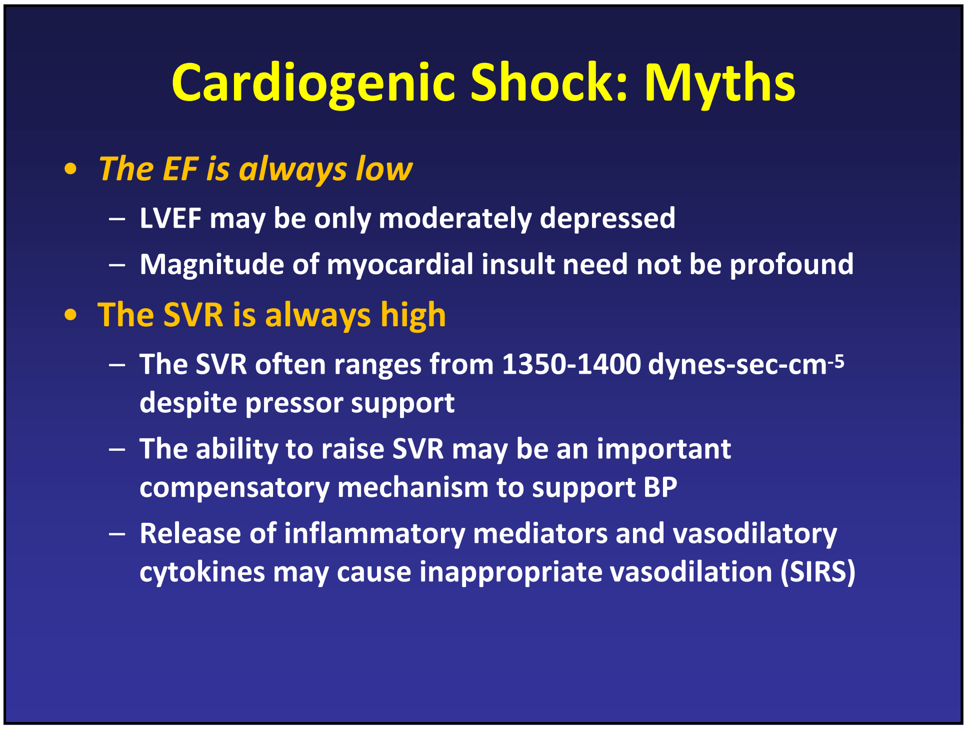
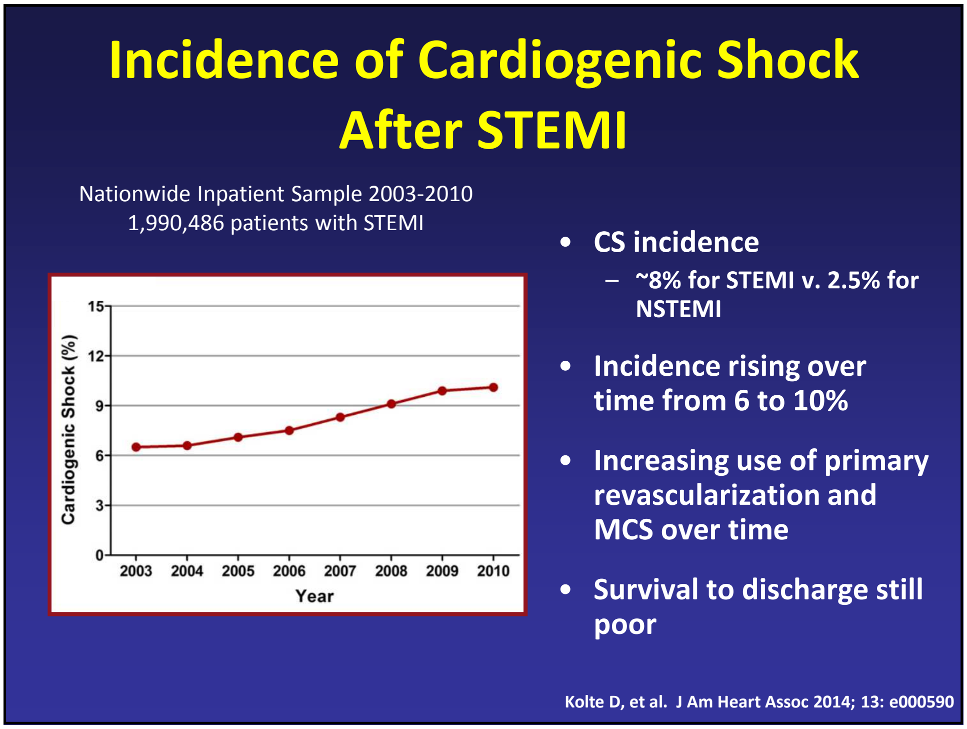


Cardiogenic Shock: Myths

- ***The EF is always low***
  - **LVEF may be only moderately depressed**
  - **Magnitude of myocardial insult need not be profound**
- **The SVR is always high**
  - **The SVR often ranges from 1350-1400 dynes-sec-cm^{-5} despite pressor support**
  - **The ability to raise SVR may be an important compensatory mechanism to support BP**
  - **Release of inflammatory mediators and vasodilatory cytokines may cause inappropriate vasodilation (SIRS)**

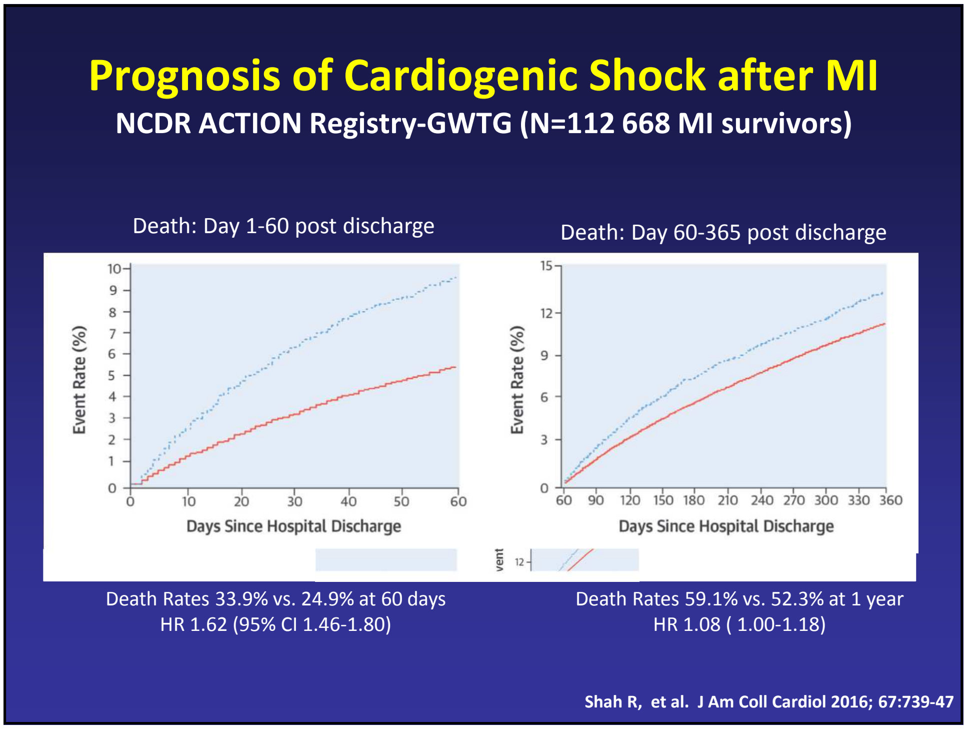


Incidence of Cardiogenic Shock After STEMI

Nationwide Inpatient Sample 2003-2010
1,990,486 patients with STEMI

- CS incidence
  - ~8% for STEMI v. 2.5% for NSTEMI
- Incidence rising over time from 6 to 10%
- Increasing use of primary revascularization and MCS over time
- Survival to discharge still poor

Kolte D, et al. J Am Heart Assoc 2014; 13: e000590



Prognosis of Cardiogenic Shock after MI

NCDR ACTION Registry-GWTG (N=112 668 MI survivors)

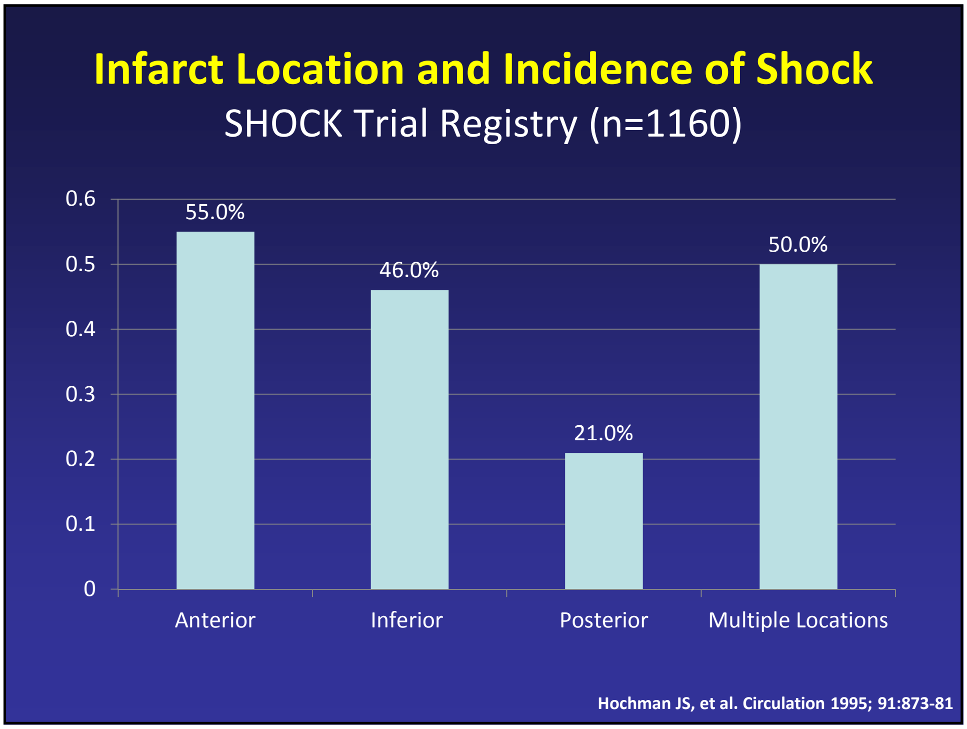
Death: Day 1-60 post discharge

Death Rates 33.9% vs. 24.9% at 60 days
HR 1.62 (95% CI 1.46-1.80)

Death: Day 60-365 post discharge

Death Rates 59.1% vs. 52.3% at 1 year
HR 1.08 (1.00-1.18)

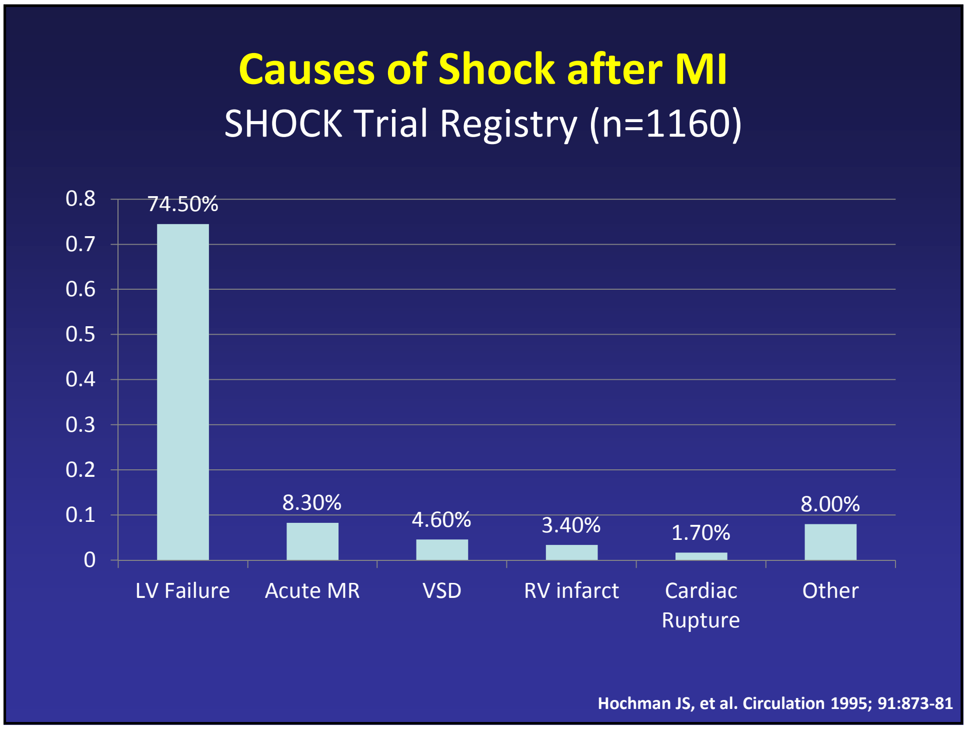
Shah R, et al. J Am Coll Cardiol 2016; 67:739-47



Infarct Location and Incidence of Shock

SHOCK Trial Registry (n=1160)

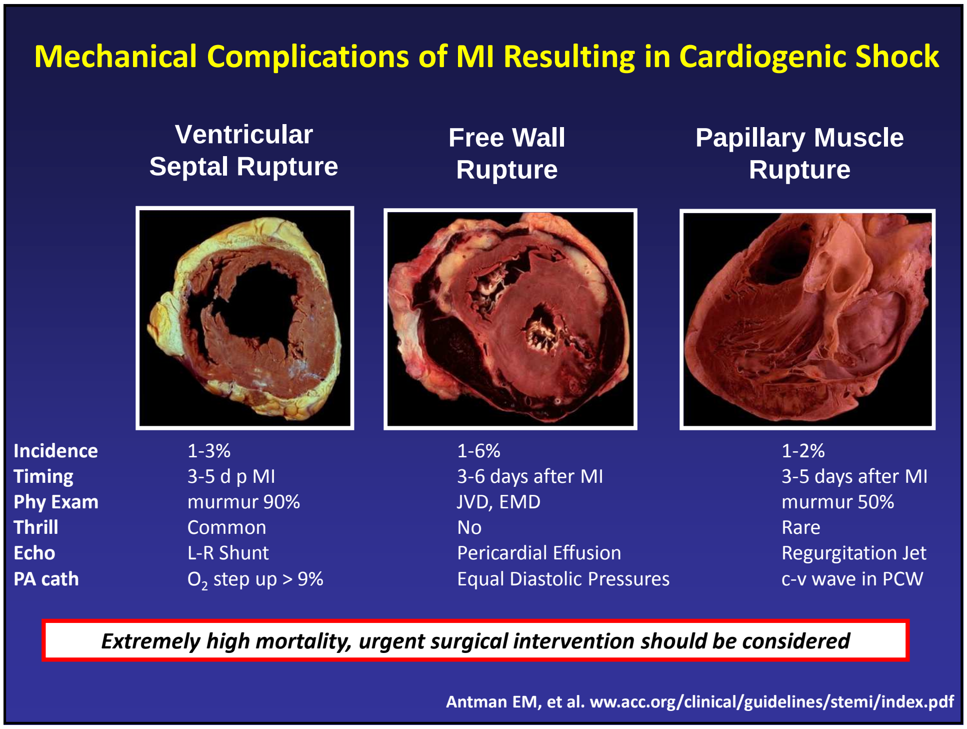
Hochman JS, et al. Circulation 1995; 91:873-81



Causes of Shock after MI

SHOCK Trial Registry (n=1160)

Hochman JS, et al. Circulation 1995; 91:873-81

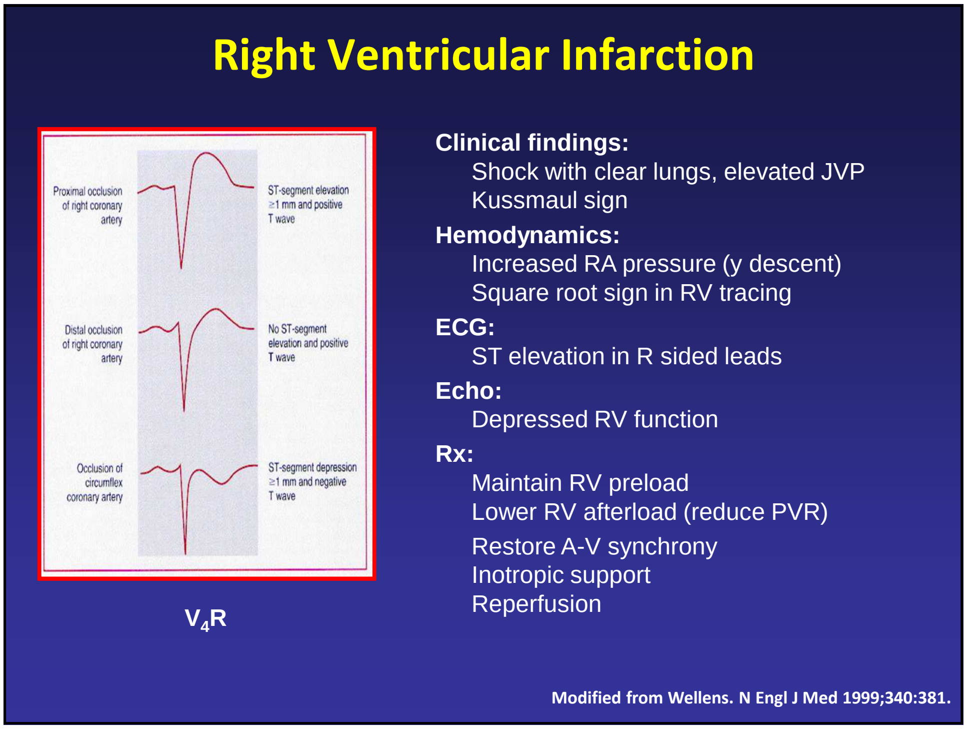


Mechanical Complications of MI Resulting in Cardiogenic Shock

	Ventricular Septal Rupture	Free Wall Rupture	Papillary Muscle Rupture
Incidence	1-3%	1-6%	1-2%
Timing	3-5 d p MI	3-6 days after MI	3-5 days after MI
Phy Exam	murmur 90%	JVD, EMD	murmur 50%
Thrill	Common	No	Rare
Echo	L-R Shunt	Pericardial Effusion	Regurgitation Jet
PA cath	O_2 step up > 9%	Equal Diastolic Pressures	c-v wave in PCW

Extremely high mortality, urgent surgical intervention should be considered

Antman EM, et al. www.acc.org/clinical/guidelines/stemi/index.pdf


Proximal occlusion of right coronary artery
ST-segment elevation ≥1 mm and positive T wave
Distal occlusion of right coronary artery
No ST-segment elevation and positive T wave
Occlusion of circumflex coronary artery
ST-segment depression ≥1 mm and negative T wave

Right Ventricular Infarction

V_4R

Clinical findings:
- Shock with clear lungs, elevated JVP
- Kussmaul sign

Hemodynamics:
- Increased RA pressure (y descent)
- Square root sign in RV tracing

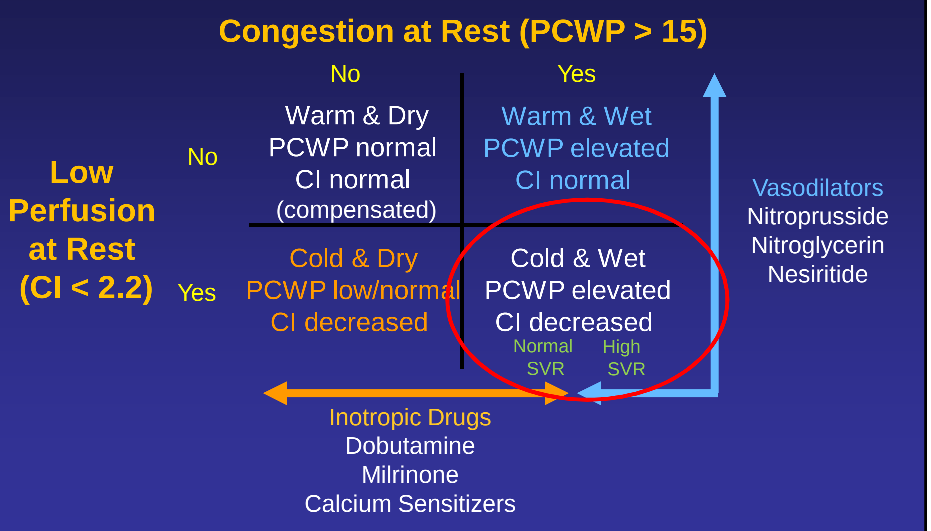
ECG:
- ST elevation in R sided leads

Echo:
- Depressed RV function

Rx:
- Maintain RV preload
- Lower RV afterload (reduce PVR)
- Restore A-V synchrony
- Inotropic support
- Reperfusion

Modified from Wellens. N Engl J Med 1999;340:381.

Patient Selection and Treatment



Congestion at Rest (PCWP > 15)

		No	Yes
Low Perfusion at Rest (CI < 2.2)	No	Warm & Dry PCWP normal CI normal (compensated)	Warm & Wet PCWP elevated CI normal
	Yes	Cold & Dry PCWP low/normal CI decreased	Cold & Wet PCWP elevated CI decreased Normal SVR High SVR

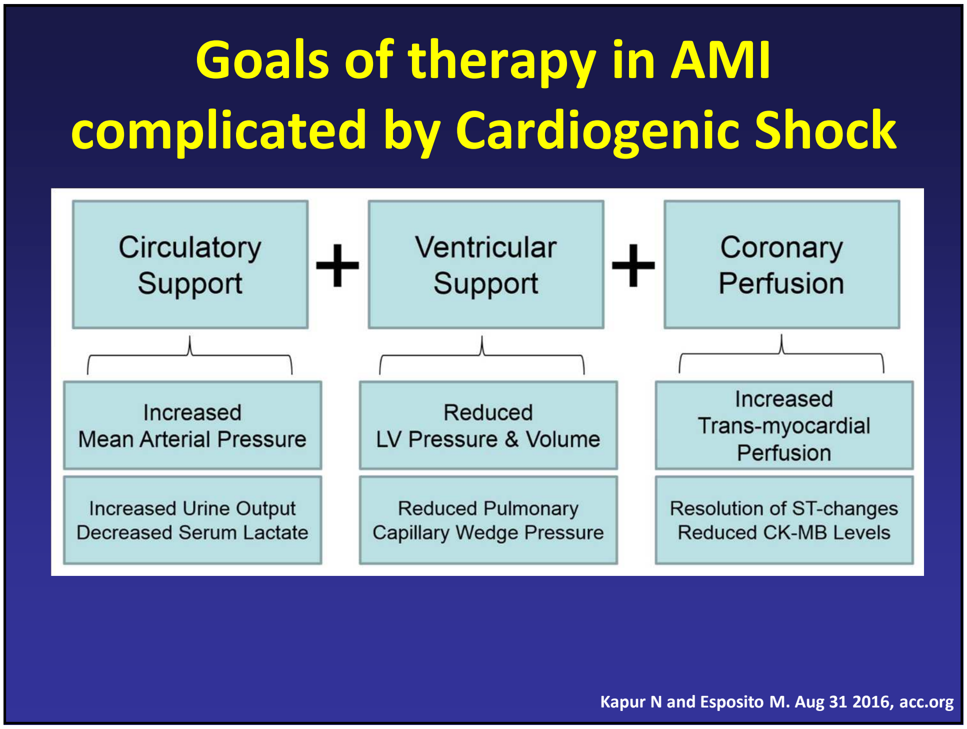
Vasodilators
Nitroprusside
Nitroglycerin
Nesiritide

Inotropic Drugs
Dobutamine
Milrinone
Calcium Sensitizers

Stevenson LW. *Eur J Heart Fail.* 1999;1:251

General Management Strategies

- Arterial pressure monitoring
- Consider PA catheter, particularly in severe hypotension
- Maintain arterial oxygenation, low threshold for mechanical ventilation
- Maintain near-normal arterial pH to minimize ischemia
- Avoid negative inotropes
- Echocardiography to evaluate for mechanical complications
- Early consideration of mechanical circulatory support and reperfusion

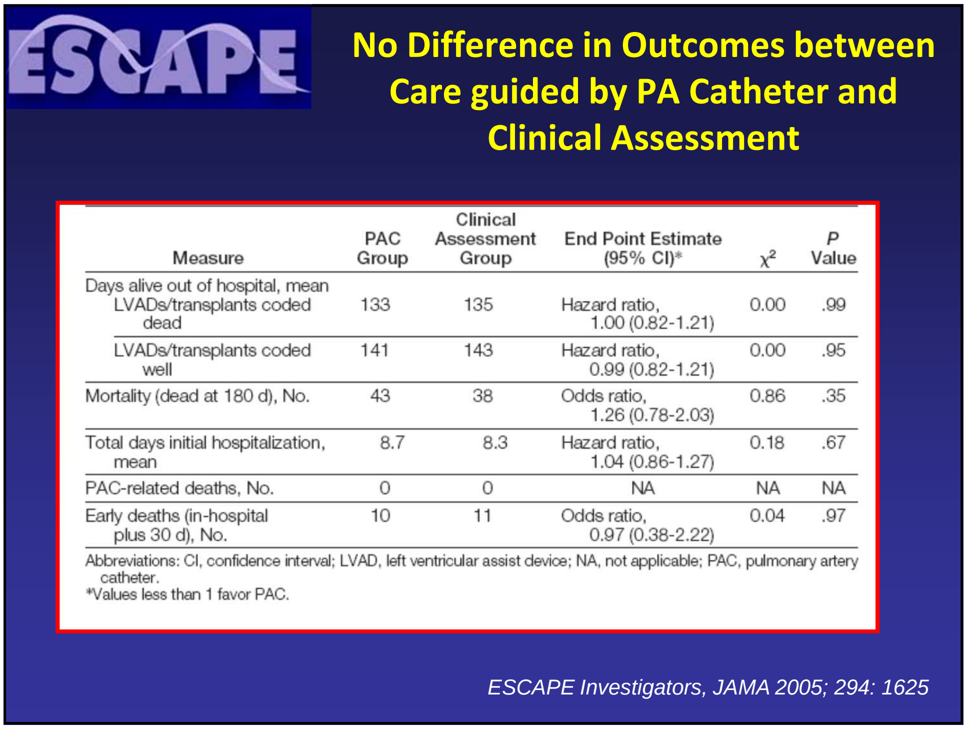


Goals of therapy in AMI complicated by Cardiogenic Shock

Circulatory Support + Ventricular Support + Coronary Perfusion

Circulatory Support	Ventricular Support	Coronary Perfusion
Increased Mean Arterial Pressure	Reduced LV Pressure & Volume	Increased Trans-myocardial Perfusion
Increased Urine Output Decreased Serum Lactate	Reduced Pulmonary Capillary Wedge Pressure	Resolution of ST-changes Reduced CK-MB Levels

Kapur N and Esposito M. Aug 31 2016, acc.org



No Difference in Outcomes between Care guided by PA Catheter and Clinical Assessment

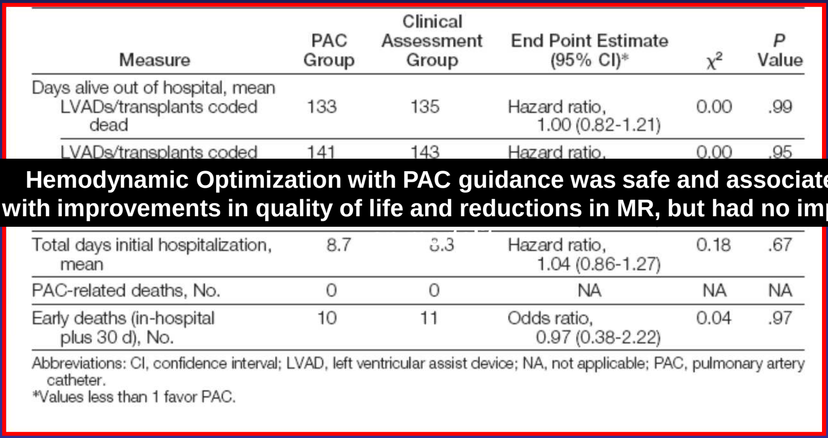
Measure	PAC Group	Clinical Assessment Group	End Point Estimate (95% CI)*	χ^2	*P* Value
Days alive out of hospital, mean					
LVADs/transplants coded dead	133	135	Hazard ratio, 1.00 (0.82-1.21)	0.00	.99
LVADs/transplants coded well	141	143	Hazard ratio, 0.99 (0.82-1.21)	0.00	.95
Mortality (dead at 180 d), No.	43	38	Odds ratio, 1.26 (0.78-2.03)	0.86	.35
Total days initial hospitalization, mean	8.7	8.3	Hazard ratio, 1.04 (0.86-1.27)	0.18	.67
PAC-related deaths, No.	0	0	NA	NA	NA
Early deaths (in-hospital plus 30 d), No.	10	11	Odds ratio, 0.97 (0.38-2.22)	0.04	.97

Abbreviations: CI, confidence interval; LVAD, left ventricular assist device; NA, not applicable; PAC, pulmonary artery catheter.
*Values less than 1 favor PAC.

ESCAPE Investigators, JAMA 2005; 294: 1625

ESCAPE

No Difference in Outcomes between Care guided by PA Catheter and Clinical Assessment



Measure	PAC Group	Clinical Assessment Group	End Point Estimate (95% CI)*	χ^2	*P* Value
Days alive out of hospital, mean LVADs/transplants coded dead	133	135	Hazard ratio, 1.00 (0.82-1.21)	0.00	.99
LVADs/transplants coded	141	143	Hazard ratio,	0.00	.95
Total days initial hospitalization, mean	8.7	8.3	Hazard ratio, 1.04 (0.86-1.27)	0.18	.67
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Abbreviations: CI, confidence interval; LVAD, left ventricular assist device; NA, not applicable; PAC, pulmonary artery catheter.

*Values less than 1 favor PAC.

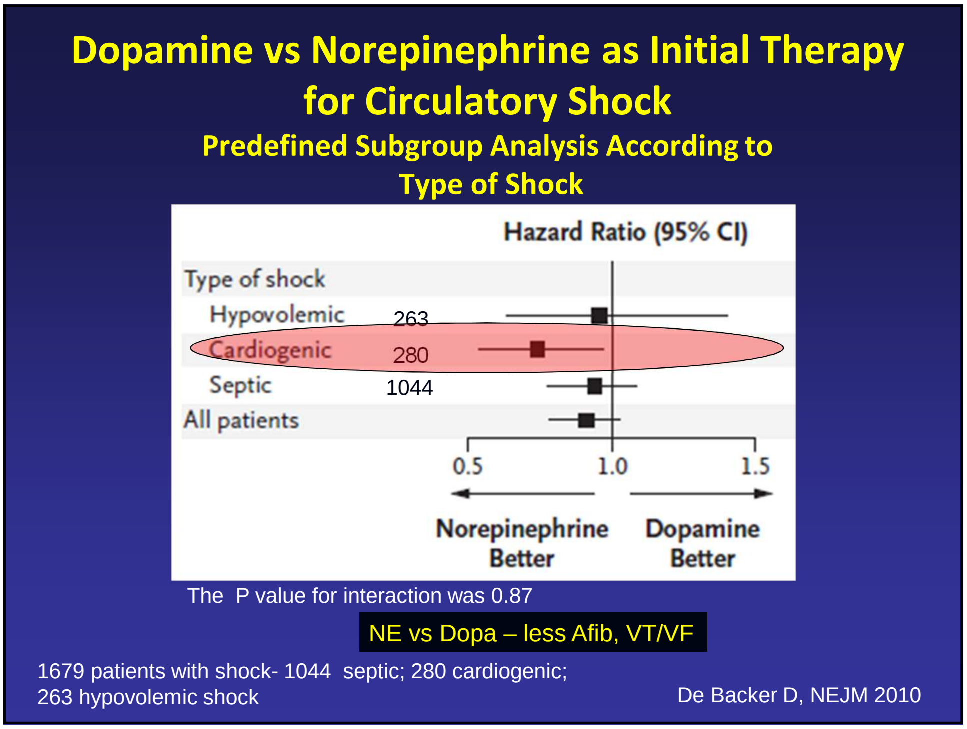
Hemodynamic Optimization with PAC guidance was safe and associated with improvements in quality of life and reductions in MR, but had no impact

ESCAPE Investigators, JAMA 2005; 294: 1625

Pharmacologic Therapy

Drug	*α$_1$*	*β$_1$*	*β$_2$*	*Heart Rate*	*Cardiac Output*	*Systemic Vascular Resistance*
Dobutamine	+	+++	++	↔↑	↑↑	↓
Dopamine						
1-2 μg/kg/min	—	—	—	↔	↔	↔
2-10 μg/kg/min	+	++	—	↑	↑↑	↔↑
10-20 μg/kg/min	+++	++	—	↑↑	↔↑	↑↑
Epinephrine	+++	++	++	↑↑	↑	↑↑
Norepinephrine	+++	++	—	↔	↔	↑↑
Phenylephrine	+++	—	—	↔	↔	↑↑

Milrinone : phosphodiesterase 3 inhibitor with similar effects to dobutamine, but more potent systemic and pulmonary vasodilation



Dopamine vs Norepinephrine as Initial Therapy for Circulatory Shock

Predefined Subgroup Analysis According to Type of Shock

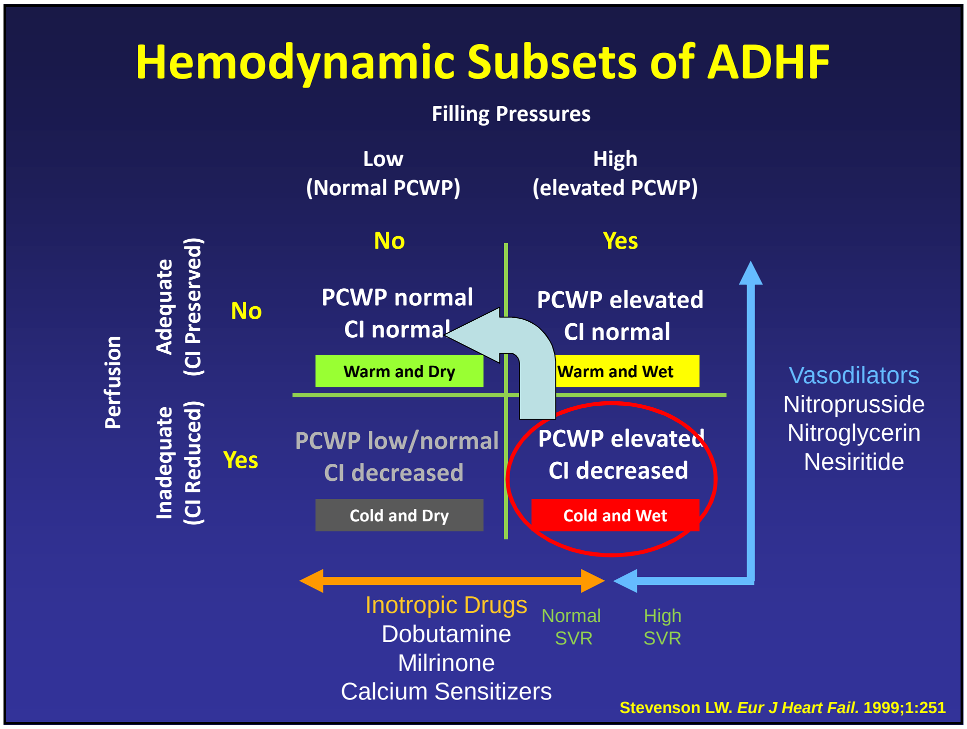
Type of shock		Hazard Ratio (95% CI)
Hypovolemic	263	
Cardiogenic	280	
Septic	1044	
All patients		

The P value for interaction was 0.87

NE vs Dopa – less Afib, VT/VF

1679 patients with shock- 1044 septic; 280 cardiogenic; 263 hypovolemic shock

De Backer D, NEJM 2010



Hemodynamic Subsets of ADHF

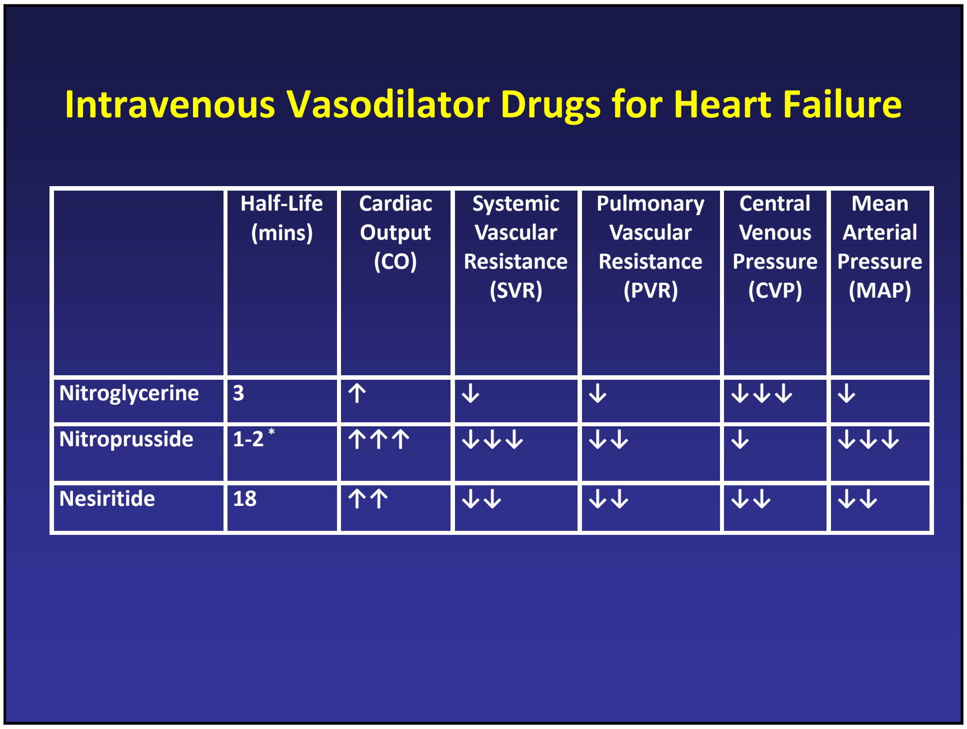
Filling Pressures

Perfusion		Low (Normal PCWP) No	High (elevated PCWP) Yes
Adequate (CI Preserved)	No	PCWP normal CI normal Warm and Dry	PCWP elevated CI normal Warm and Wet
Inadequate (CI Reduced)	Yes	PCWP low/normal CI decreased Cold and Dry	PCWP elevated CI decreased Cold and Wet

Vasodilators
Nitroprusside
Nitroglycerin
Nesiritide

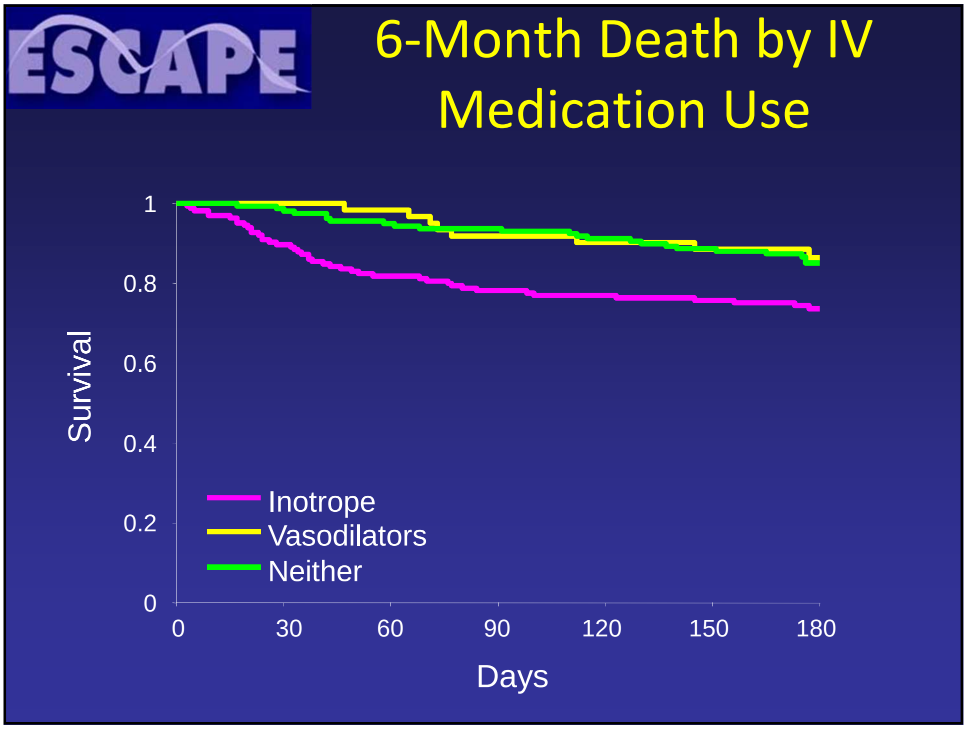
Inotropic Drugs
Dobutamine
Milrinone
Calcium Sensitizers

Stevenson LW. *Eur J Heart Fail.* 1999;1:251

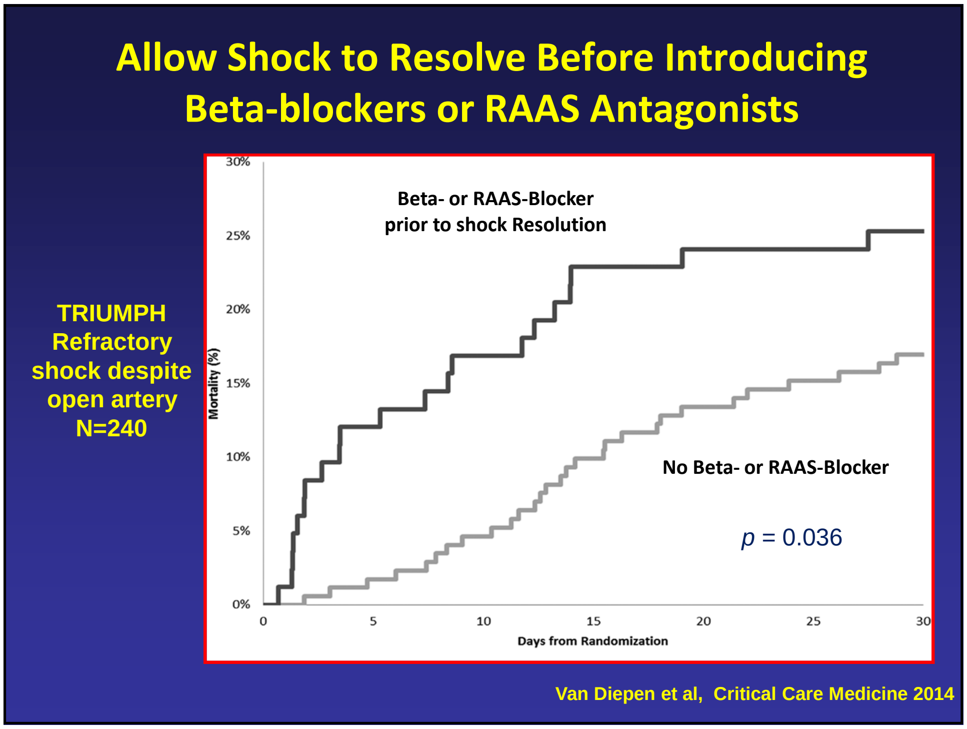


Intravenous Vasodilator Drugs for Heart Failure

	Half-Life (mins)	Cardiac Output (CO)	Systemic Vascular Resistance (SVR)	Pulmonary Vascular Resistance (PVR)	Central Venous Pressure (CVP)	Mean Arterial Pressure (MAP)
Nitroglycerine	3	↑	↓	↓	↓↓↓	↓
Nitroprusside	1-2*	↑↑↑	↓↓↓	↓↓	↓	↓↓↓
Nesiritide	18	↑↑	↓↓	↓↓	↓↓	↓↓



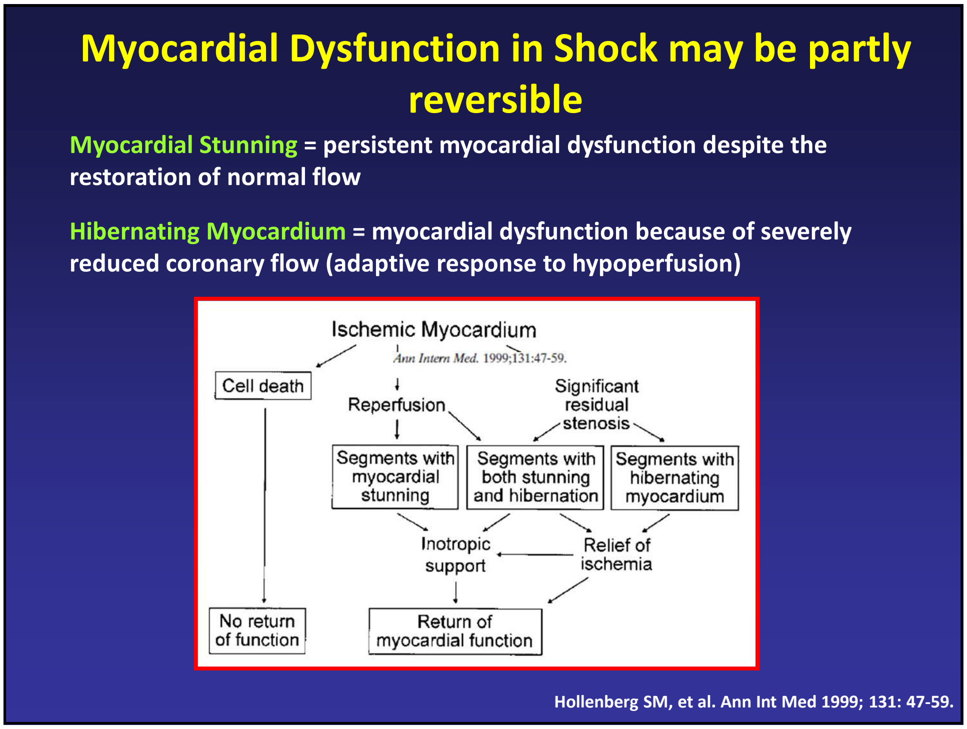
6-Month Death by IV Medication Use



Allow Shock to Resolve Before Introducing Beta-blockers or RAAS Antagonists

TRIUMPH
Refractory shock despite open artery
N=240

Van Diepen et al, Critical Care Medicine 2014



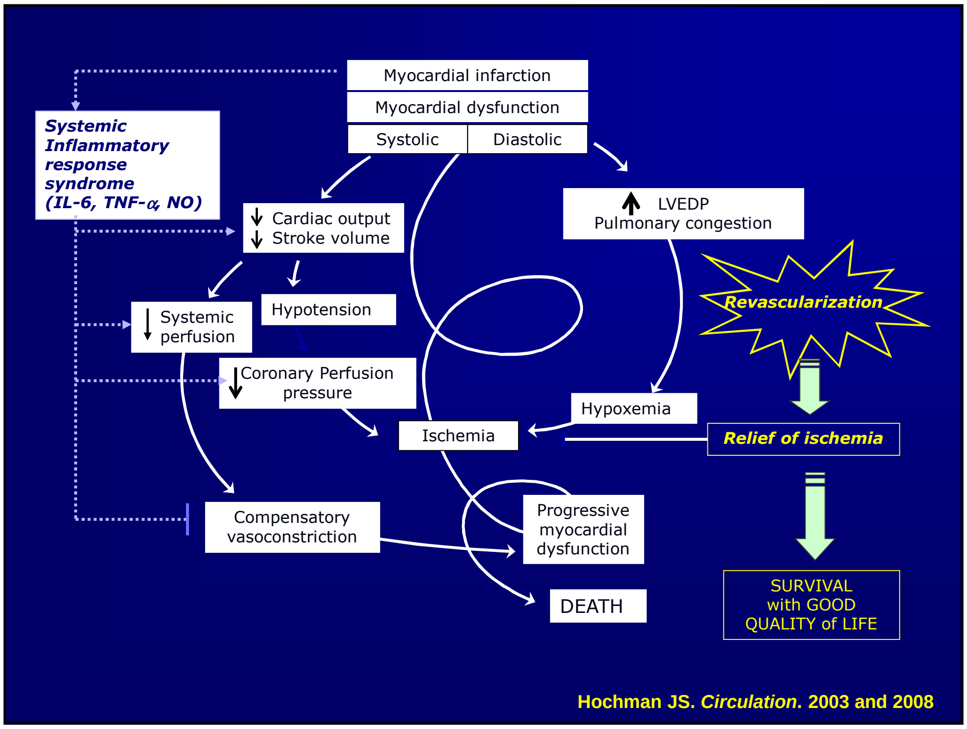
Myocardial Dysfunction in Shock may be partly reversible

Myocardial Stunning = persistent myocardial dysfunction despite the restoration of normal flow

Hibernating Myocardium = myocardial dysfunction because of severely reduced coronary flow (adaptive response to hypoperfusion)

Ischemic Myocardium
Ann Intern Med. 1999;131:47-59.
Cell death
Reperfusion
Significant residual stenosis
Segments with myocardial stunning
Segments with both stunning and hibernation
Segments with hibernating myocardium
Inotropic support
Relief of ischemia
No return of function
Return of myocardial function

Hollenberg SM, et al. Ann Int Med 1999; 131: 47-59.



Myocardial infarction

Myocardial dysfunction

Systolic | Diastolic

Systemic Inflammatory response syndrome (IL-6, TNF-α, NO)

↓ Cardiac output
↓ Stroke volume

↑ LVEDP
Pulmonary congestion

Revascularization

↓ Systemic perfusion

Hypotension

↓ Coronary Perfusion pressure

Hypoxemia

Ischemia

Relief of ischemia

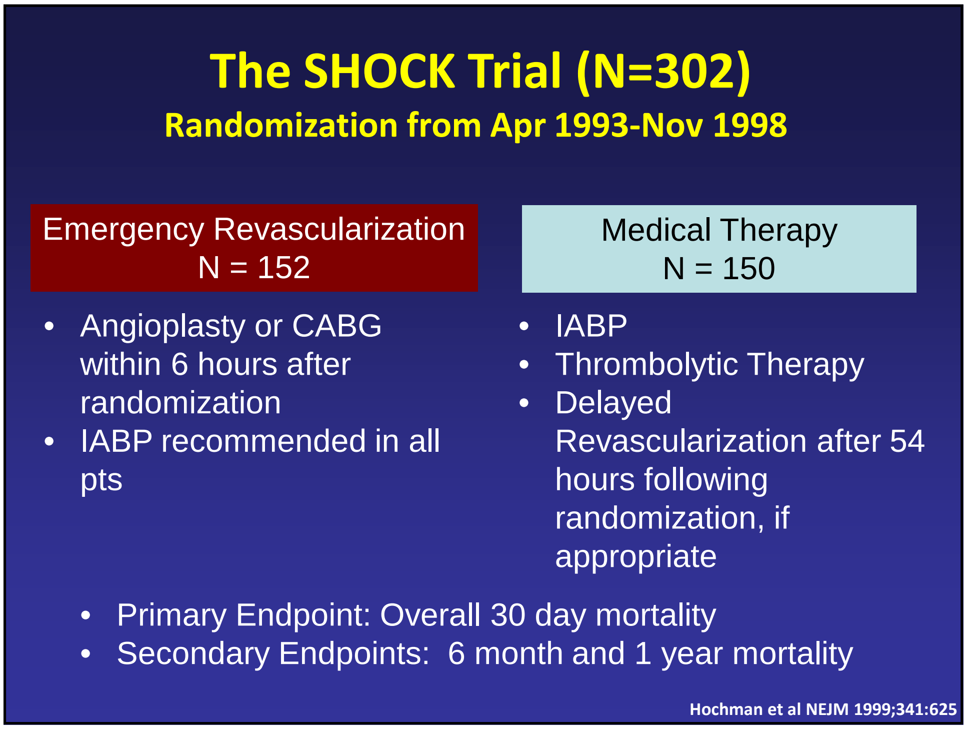
Compensatory vasoconstriction

Progressive myocardial dysfunction

DEATH

SURVIVAL
with GOOD
QUALITY of LIFE

Hochman JS. *Circulation*. 2003 and 2008



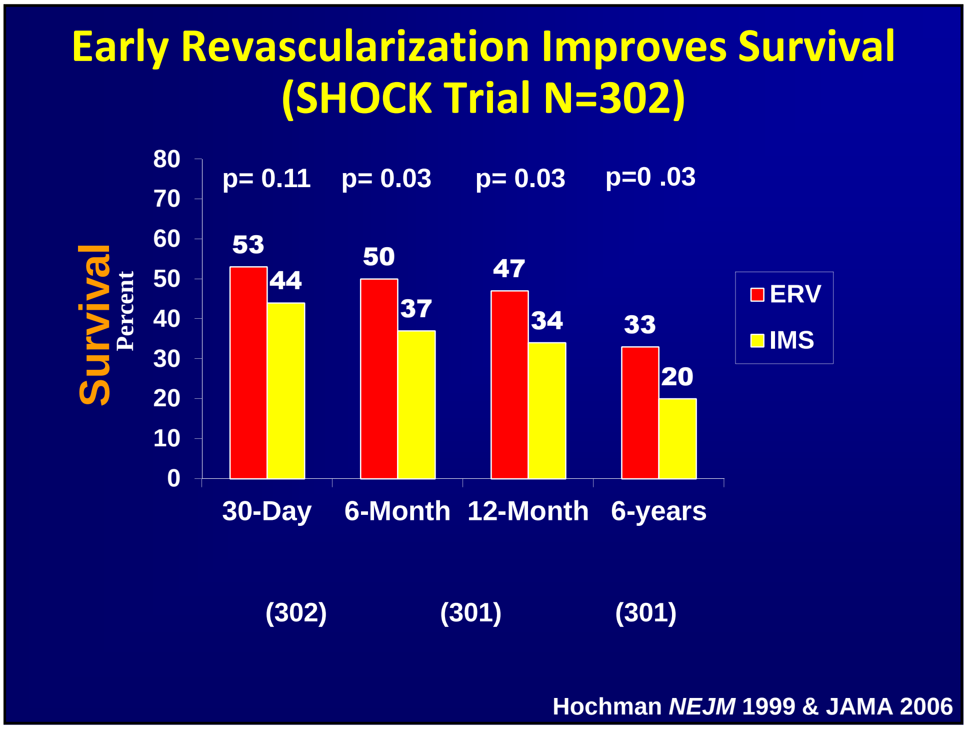
The SHOCK Trial (N=302)

Randomization from Apr 1993-Nov 1998

Emergency Revascularization N = 152	Medical Therapy N = 150
• Angioplasty or CABG within 6 hours after randomization • IABP recommended in all pts	• IABP • Thrombolytic Therapy • Delayed Revascularization after 54 hours following randomization, if appropriate

- Primary Endpoint: Overall 30 day mortality
- Secondary Endpoints: 6 month and 1 year mortality

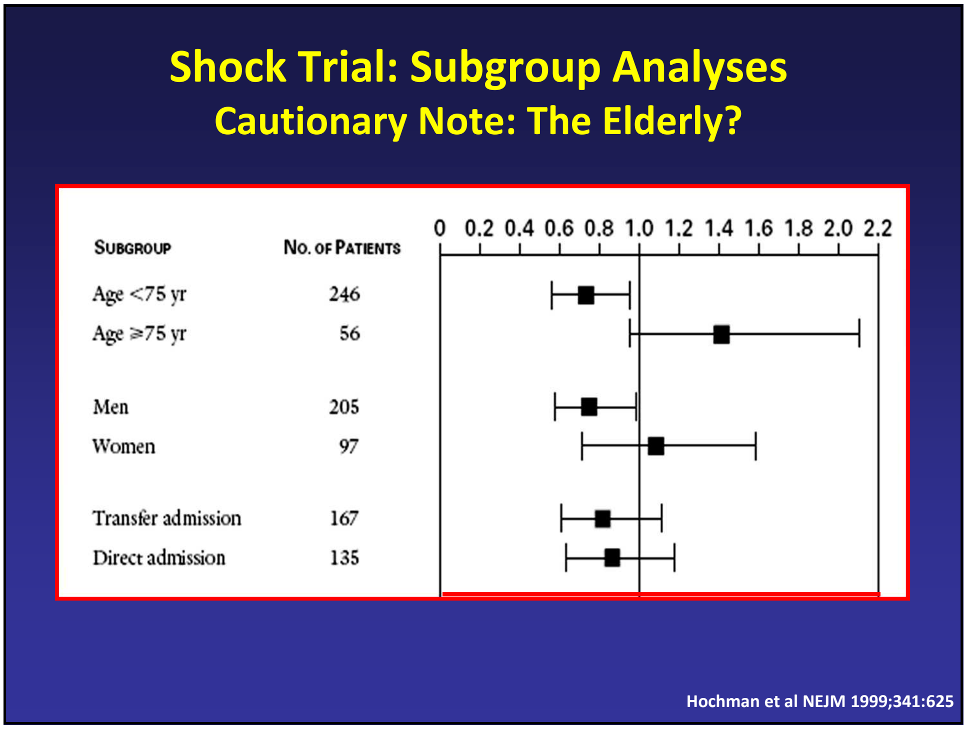
Hochman et al NEJM 1999;341:625



Early Revascularization Improves Survival (SHOCK Trial N=302)

(302) (301) (301)

Hochman *NEJM* 1999 & JAMA 2006



Shock Trial: Subgroup Analyses
Cautionary Note: The Elderly?

SUBGROUP	NO. OF PATIENTS
Age <75 yr	246
Age ≥75 yr	56
Men	205
Women	97
Transfer admission	167
Direct admission	135

Hochman et al NEJM 1999;341:625

2013 ACC/AHA STEMI Guidelines: Cardiogenic Shock Management

Class I Recommendations (Should do)

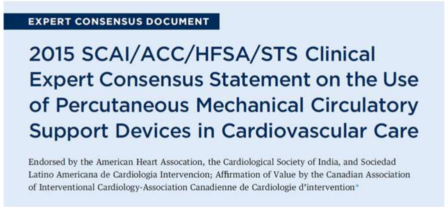
1. Emergency revascularization with either PCI or CABG is recommended in suitable patients with cardiogenic shock due to pump failure after STEMI irrespective of the time delay from MI onset. (*Level of Evidence: B*)

1. In the absence of contraindications,fibrinolytic therapy should be administered to patients with STEMI and cardiogenic shock who are unsuitable candidates for either PCI or CABG. (*Level of Evidence: B*)

O'Gara PT, et al. Circulation 2013; 127:e362-e425.

Potential Benefits of MCS in Cardiogenic Shock

- Maintain End-Organ Perfusion
- Reduce Intracardiac Filling Pressures
- Reduce ventricular volumes, wall stress, and myocardial oxygen consumption
- Augment coronary perfusion
- Limit Infarct Size

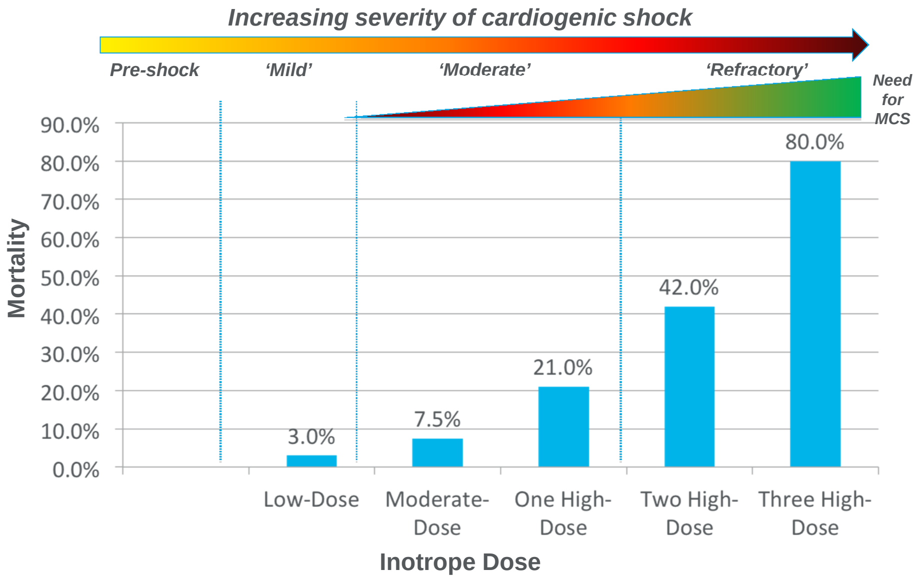


EXPERT CONSENSUS DOCUMENT

2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care

Endorsed by the American Heart Assocation, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention[*]

Rihal, et al. J Am Coll Cardiol 2015; 65: e7-26.



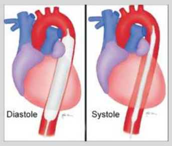
Kar, et al. Circulation 2012; 125: 1809-1817.

Options for Temporary MCS

*LV Support Only**

Percutaneous

IABP



Impella

TandemHeart

ECMO

Less Support *More support*

Surgically Implanted

TandemHeart

Abiomed BVS 5000

Centrimag

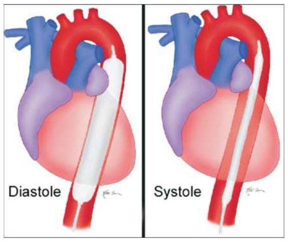
ECMO

Considerations in Device Selection

- **Etiology of Shock**
- **Anticipated Duration of Support**
- **Left Ventricular Support, Right Ventricular Support, or Both?**
- **What is the Goal?**
  - **Bridge to Recovery**
  - **Bridge to Durable VAD**
  - **Bridge to Transplant**
  - **Bridge to Decision**

Intra-Aortic Balloon Counterpulsation (IABP)

- Traditional mainstay of mechanical therapy for cardiogenic shock
- Inflates in diastole
  - Augments coronary and peripheral perfusion
- Deflates in systole
  - Reduces afterload
- Effective in acute hemodynamic stabilization, though no definitive impact on mortality in shock
- Patients with a good hemodynamic response to IABP experience better outcome[2]



Willerson JT, et al. Am J Med 1975; 58: 183-91
Ramanathan K, et al. Circulation 2003; 108(suppl I): I-672

Use of IABP

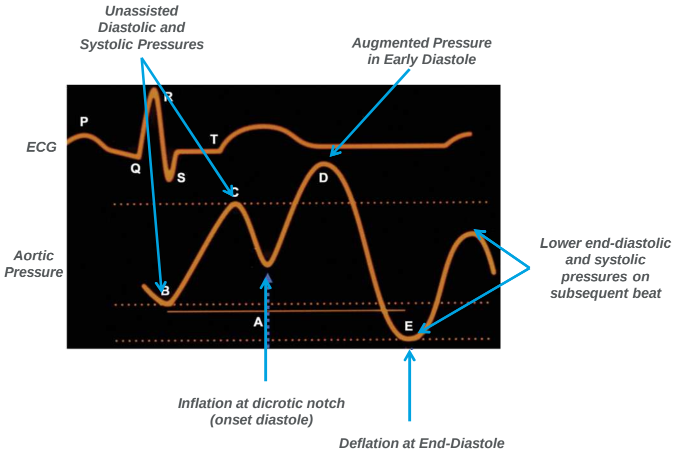
Consider for

- patients with STEMI when cardiogenic shock is not rapidly reversed with pharmacologic therapy
- inotrope-refractory heart failure in patients with cardiomyopathy
- Medically refractory ventricular tachycardia
- Mechanical MI complication (VSD, Papillary muscle rupture)

Contraindications

- Significant AI
- Severe PAD
- Abdominal aortic aneurysm
- Aortic Dissection

IABP Timing



Unassisted Diastolic and Systolic Pressures

Augmented Pressure in Early Diastole

Lower end-diastolic and systolic pressures on subsequent beat

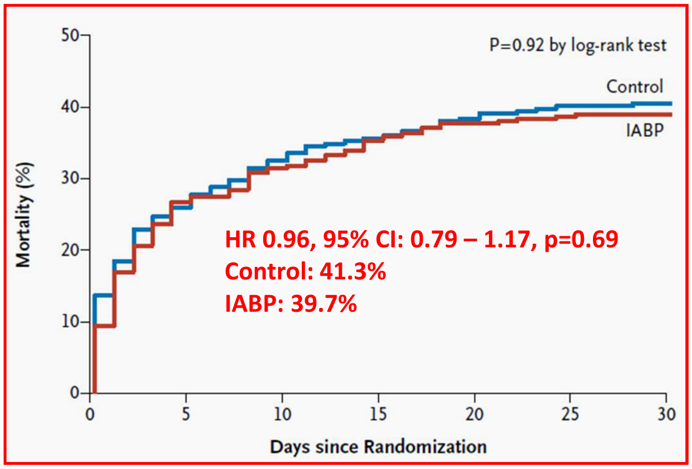
Inflation at dicrotic notch (onset diastole)

Deflation at End-Diastole

Krishna and Zacharowski, Contin Educ Anaesth Crit Care Pain 2009;9:24-28

IABP SHOCK-2 Trial

30-Day Mortality



HR 0.96, 95% CI: 0.79 – 1.17, p=0.69
Control: 41.3%
IABP: 39.7%

Thiele et al, NEJM 2012

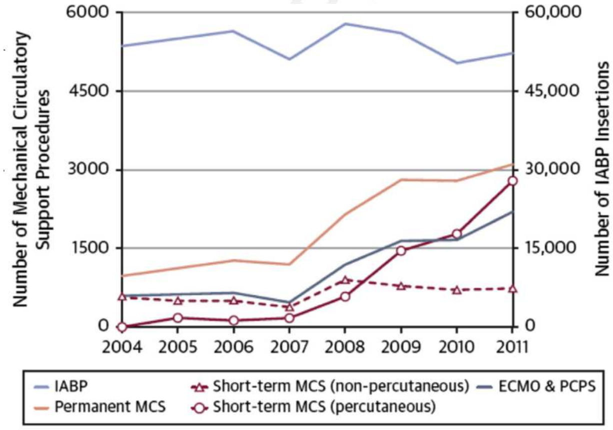
Physiological Effects of IABP

Cardiac Index (L/min/M²)	↑ 40%
Arterial Lactate (mmol/L)	↓ 42%
Coronary Blood Flow (M²/100g/min)	↑ 34%

Cardiac Output	↑ 500 ml/min
Heart Rate	↓ 7 bts/min
Systolic BP	↓ 20 mmHg
Diastolic BP	↑ 30 mmHg

Sheidt, NEJM 1973; Mueller, Circ 1972

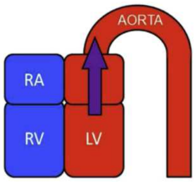
Trends in MCS Use

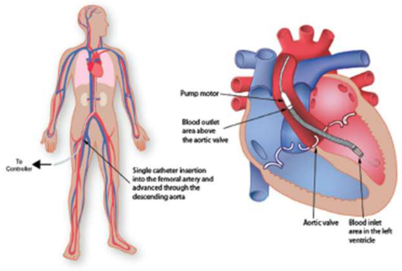


Kapur and Esposito, Heart Failure Clinics 2015

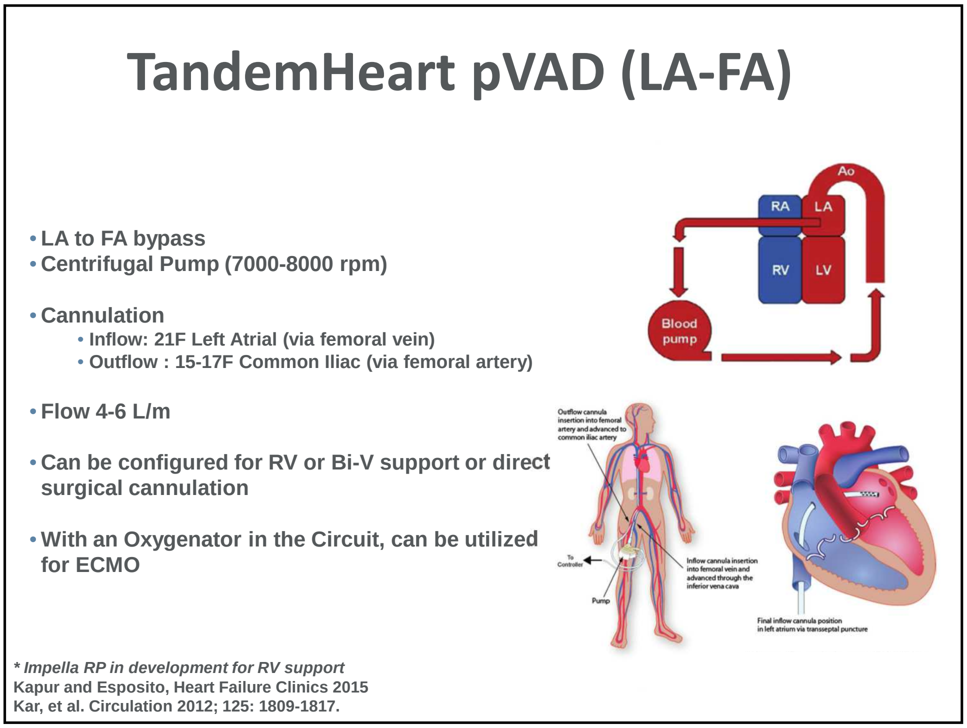
Impella pVAD (LV-Ao)

- Micro Axial Flow Pump (25000-30000 rpm)
- Retrograde cannulation of LV via FA
  - 12-14 F Arterial Access
- Flow of 2.5 or 4.0 L/min (or 5.0 L/min with surgical cutdown) depending on device
- LV support only*


AORTA
RA
RV
LV


To Controller
Single catheter insertion into the femoral artery and advanced through the descending aorta
Pump motor
Blood outlet area above the aortic valve
Aortic valve
Blood inlet area in the left ventricle

•Impella RP in development for RV support
•Heartmate PHP under investigation in Europe, similar principle
Kapur and Esposito, Heart Failure Clinics 2015
Kar, et al. Circulation 2012; 125: 1809-1817.



TandemHeart pVAD (LA-FA)

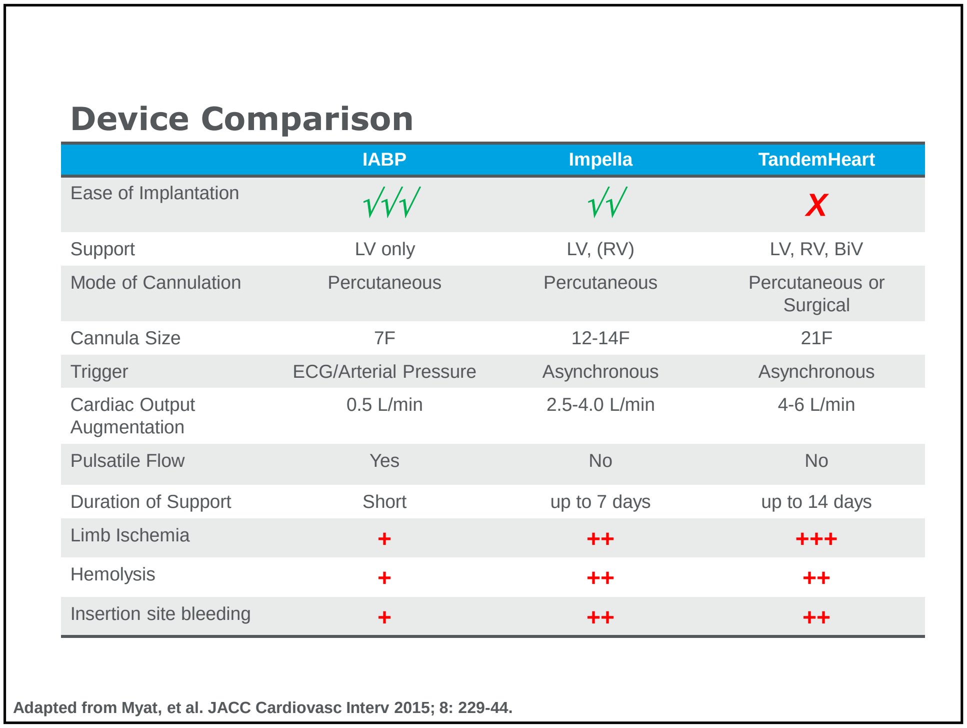
- LA to FA bypass
- Centrifugal Pump (7000-8000 rpm)
- Cannulation
  - Inflow: 21F Left Atrial (via femoral vein)
  - Outflow : 15-17F Common Iliac (via femoral artery)
- Flow 4-6 L/m
- Can be configured for RV or Bi-V support or direct surgical cannulation
- With an Oxygenator in the Circuit, can be utilized for ECMO

Ao
RA
LA
RV
LV
Blood pump
Outflow cannula insertion into femoral artery and advanced to common iliac artery
To Controller
Pump
Inflow cannula insertion into femoral vein and advanced through the inferior vena cava
Final inflow cannula position in left atrium via transseptal puncture

** Impella RP in development for RV support*

Kapur and Esposito, Heart Failure Clinics 2015

Kar, et al. Circulation 2012; 125: 1809-1817.



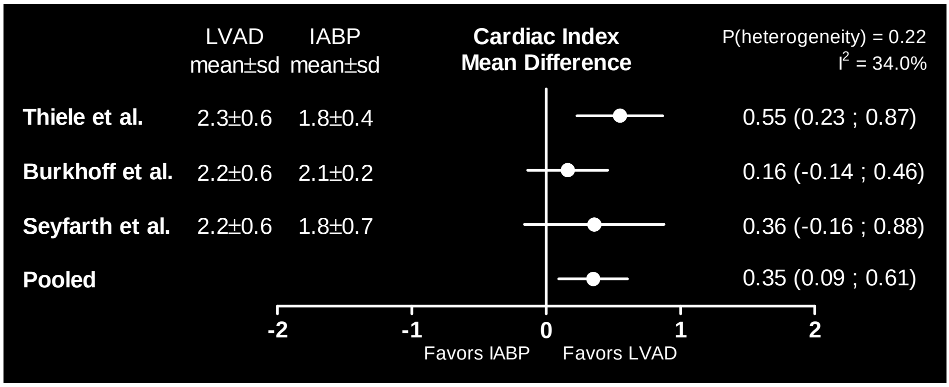
Device Comparison

	IABP	Impella	TandemHeart
Ease of Implantation	√√√	√√	X
Support	LV only	LV, (RV)	LV, RV, BiV
Mode of Cannulation	Percutaneous	Percutaneous	Percutaneous or Surgical
Cannula Size	7F	12-14F	21F
Trigger	ECG/Arterial Pressure	Asynchronous	Asynchronous
Cardiac Output Augmentation	0.5 L/min	2.5-4.0 L/min	4-6 L/min
Pulsatile Flow	Yes	No	No
Duration of Support	Short	up to 7 days	up to 14 days
Limb Ischemia	+	++	+++
Hemolysis	+	++	++
Insertion site bleeding	+	++	++

Adapted from Myat, et al. JACC Cardiovasc Interv 2015; 8: 229-44.

IABP vs Percutaneous LVAD

Cardiac Index



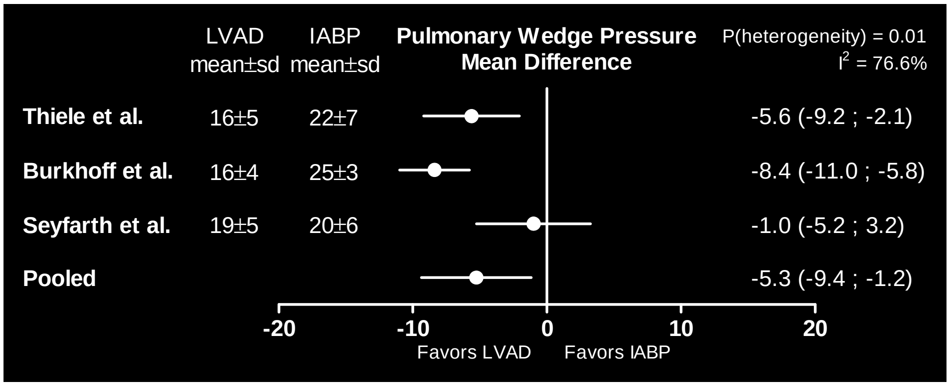
	LVAD mean±sd	IABP mean±sd	Cardiac Index Mean Difference
Thiele et al.	2.3±0.6	1.8±0.4	0.55 (0.23 ; 0.87)
Burkhoff et al.	2.2±0.6	2.1±0.2	0.16 (-0.14 ; 0.46)
Seyfarth et al.	2.2±0.6	1.8±0.7	0.36 (-0.16 ; 0.88)
Pooled			0.35 (0.09 ; 0.61)

P(heterogeneity) = 0.22
I^2 = 34.0%

Cheng et al: EHJ 2009; 30:2102

IABP vs Percutaneous LVAD

Pulmonary Capillary Wedge Pressure



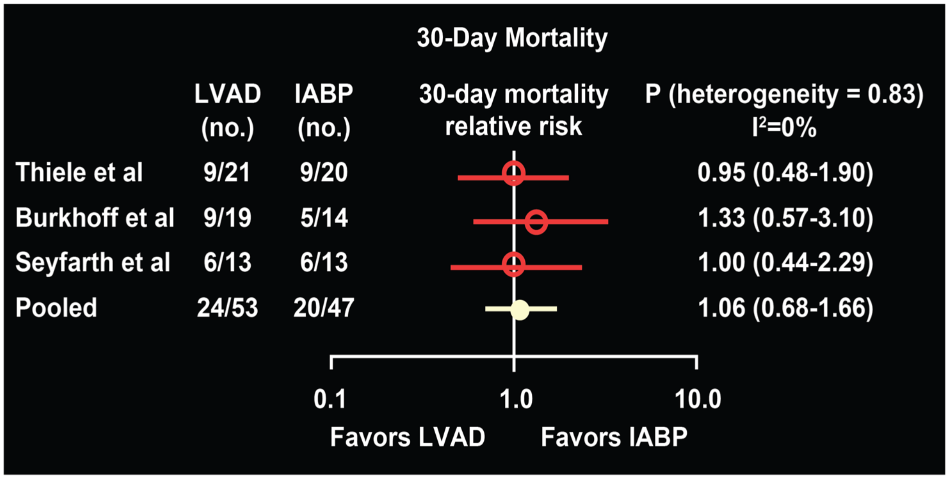
	LVAD mean±sd	IABP mean±sd	Pulmonary Wedge Pressure Mean Difference
Thiele et al.	16±5	22±7	-5.6 (-9.2 ; -2.1)
Burkhoff et al.	16±4	25±3	-8.4 (-11.0 ; -5.8)
Seyfarth et al.	19±5	20±6	-1.0 (-5.2 ; 3.2)
Pooled			-5.3 (-9.4 ; -1.2)

P(heterogeneity) = 0.01
I^2 = 76.6%

Cheng et al: EHJ 2009; 30:2102

IABP vs Percutaneous LVAD

30 Day Mortality



30-Day Mortality

	LVAD (no.)	IABP (no.)	30-day mortality relative risk	P (heterogeneity = 0.83) I^2=0%
Thiele et al	9/21	9/20		0.95 (0.48-1.90)
Burkhoff et al	9/19	5/14		1.33 (0.57-3.10)
Seyfarth et al	6/13	6/13		1.00 (0.44-2.29)
Pooled	24/53	20/47		1.06 (0.68-1.66)

Cheng et al: EHJ 2009; 30:2102

30-year old female at 37 weeks' gestation of a previously uncomplicated pregnancy presents with a 3-day history of pleuritic chest pain. Upon admission, due to concern for fetal distress she is taken to urgent Caesarean section without obstetrical complication. On closure of the abdomen, she suffers complete cardiovascular collapse with PEA arrest. Cardiopulmonary resuscitation is initiated with recovery of spontaneous circulation within 20 minutes. Blood pressure is 80/60 with PaO2 40 mm Hg despite an FIO2 of 1.0. the extremities are mottled and clammy. You are called to discuss options for urgent mechanical circulatory support for stabilization.

Which of the following is the best strategy?

A.Intra-aortic Balloon Pump

B.Veno-Venous ECMO

C.Veno-Arterial ECMO

D.Percutaneous Right Ventricular Assist Device

E.Percutaneous Left Ventricular Assist Device

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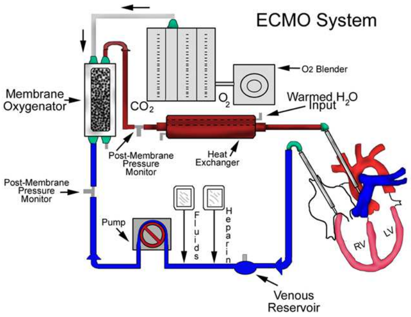
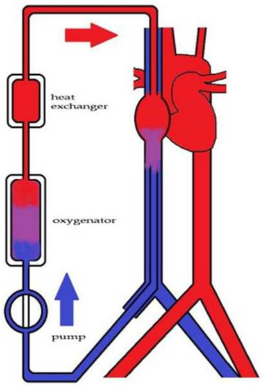
Extra-Corporeal Membrane Oxygenation

- Centrifugal, non-pulsatile pump for blood propulsion linked to a membrane oxygenator for gas exchange
- 2 broad configurations
    - Veno-Venous → Oxygenation/pulmonary support
    - Veno-Arterial → Cardiopulmonary Support
- Cannulation at bedside without fluoroscopic guidance
- ≥ 4.5 L/min depending on cannula size
    - Inflow: RA via femoral vein (18-31 F)
    - Outflow: Descending aorta via femoral artery (15-22
- Anticoagulation required (ACT 180-250)

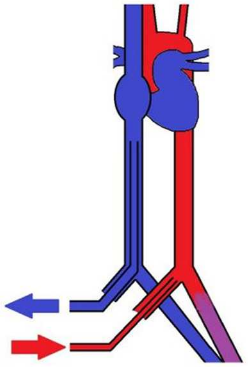

ECMO System
O2 Blender
Membrane Oxygenator
CO_2
O_2
Warmed H_2O Input
Post-Membrane Pressure Monitor
Heat Exchanger
Post-Membrane Pressure Monitor
Pump
Fluids
Heparin
RV
LV
Venous Reservoir

Cheng R, et al. Ann Thorac Surg 2014; 97(2): 610-16
Kapur and Esposito, Heart Failure Clinics 2015

ECMO Configurations



Veno-Venous ECMO
(Pulmonary Blood Flow Intact)



Veno-Arterial ECMO
(Cardiopulmonary Bypass)

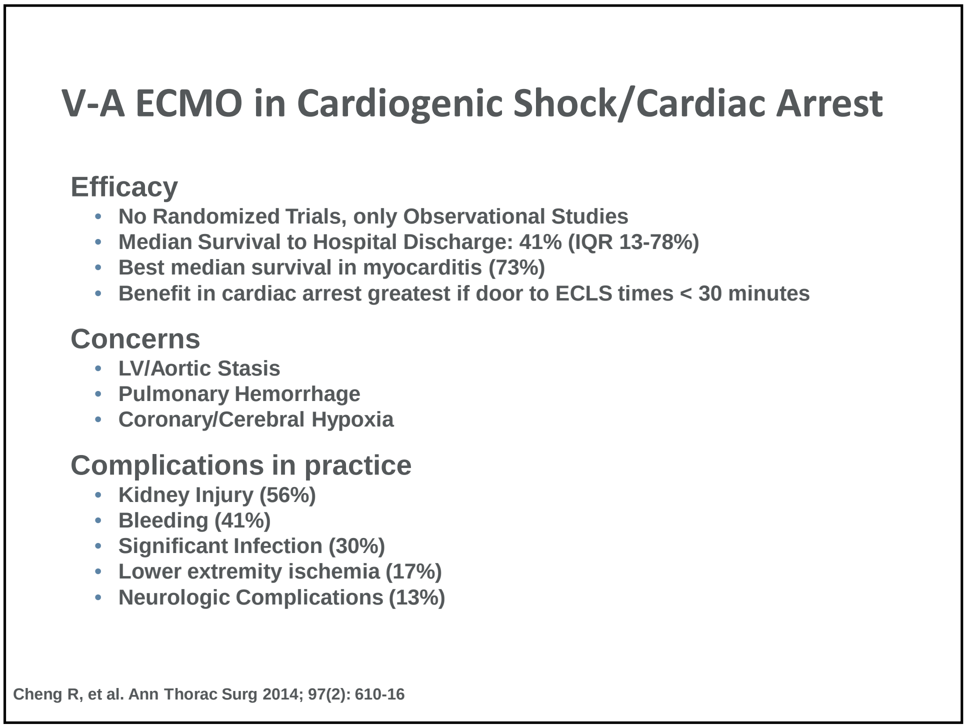
ECMO: Accepted Indications

V-V ECMO

- Hypoxemic respiratory failure with PaO_2/FiO_2 of <100 mmHg despite optimization of the ventilator settings, including the tidal volume, positive end-expiratory pressure (PEEP), and inspiratory to expiratory (I:E) ratio
  - Avoid in those mechanically ventilated for > 7 days
- Hypercapnic respiratory failure with an arterial pH less than 7.20

V-A ECMO

- Refractory cardiogenic shock
- Cardiac arrest
- Failure to wean from cardiopulmonary bypass after cardiac surgery
- As a bridge to either cardiac transplantation or placement of a ventricular assist device



V-A ECMO in Cardiogenic Shock/Cardiac Arrest

Efficacy

- No Randomized Trials, only Observational Studies
- Median Survival to Hospital Discharge: 41% (IQR 13-78%)
- Best median survival in myocarditis (73%)
- Benefit in cardiac arrest greatest if door to ECLS times < 30 minutes

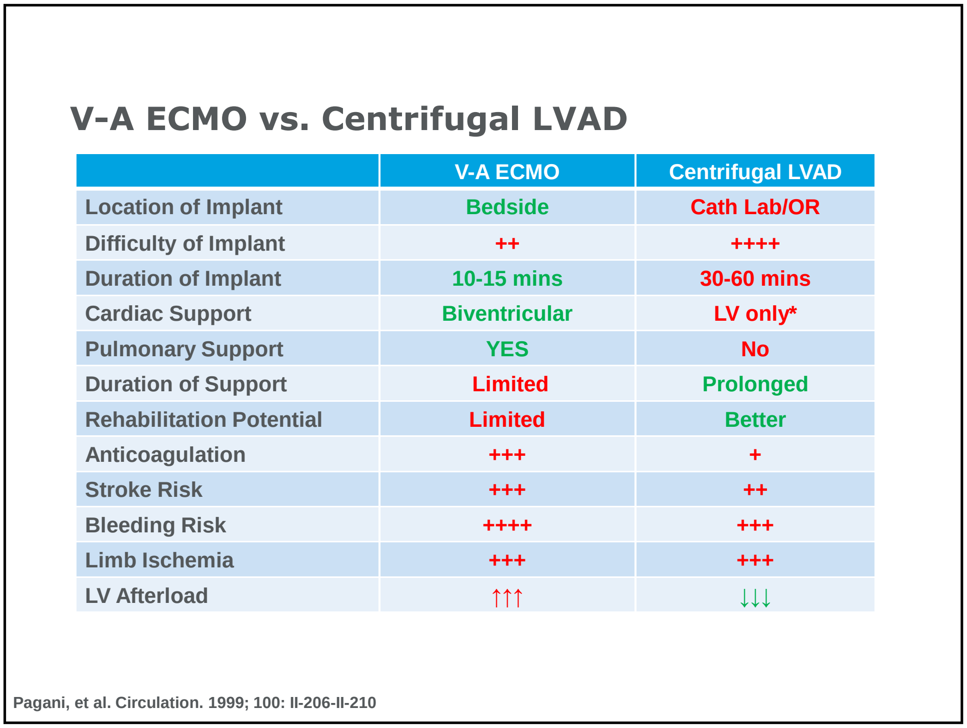
Concerns

- LV/Aortic Stasis
- Pulmonary Hemorrhage
- Coronary/Cerebral Hypoxia

Complications in practice

- Kidney Injury (56%)
- Bleeding (41%)
- Significant Infection (30%)
- Lower extremity ischemia (17%)
- Neurologic Complications (13%)

Cheng R, et al. Ann Thorac Surg 2014; 97(2): 610-16



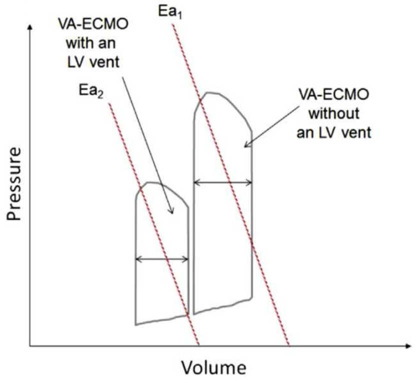
V-A ECMO vs. Centrifugal LVAD

	V-A ECMO	Centrifugal LVAD
Location of Implant	Bedside	Cath Lab/OR
Difficulty of Implant	++	++++
Duration of Implant	10-15 mins	30-60 mins
Cardiac Support	Biventricular	LV only*
Pulmonary Support	YES	No
Duration of Support	Limited	Prolonged
Rehabilitation Potential	Limited	Better
Anticoagulation	+++	+
Stroke Risk	+++	++
Bleeding Risk	++++	+++
Limb Ischemia	+++	+++
LV Afterload	↑↑↑	↓↓↓

Pagani, et al. Circulation. 1999; 100: II-206-II-210

LV Decompression during V-A ECMO for CS

- Displacement of venous blood into arterial circulation increases LV afterload
- LV decompression typically necessary to limit LV distension/stasis, pulmonary hypertension, LV thrombosis



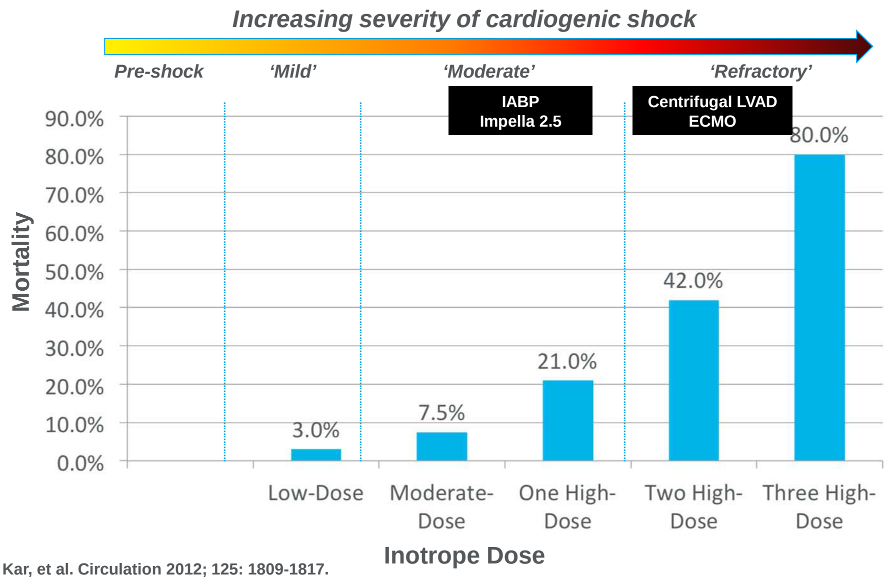
Left Heart Decompression Strategies During VA-ECMO

Percutaneous	IABP Impella axial flow catheter Transseptal left ventricular cannulation Transseptal LA cannulation Atrial septostomy
Surgical	Direct left ventricular apical cannulation Direct LA cannulation
Noninvasive	Inotropic support Reducing VA-ECMO flow

Kapur and Esposito, Heart Failure Clinics 2015

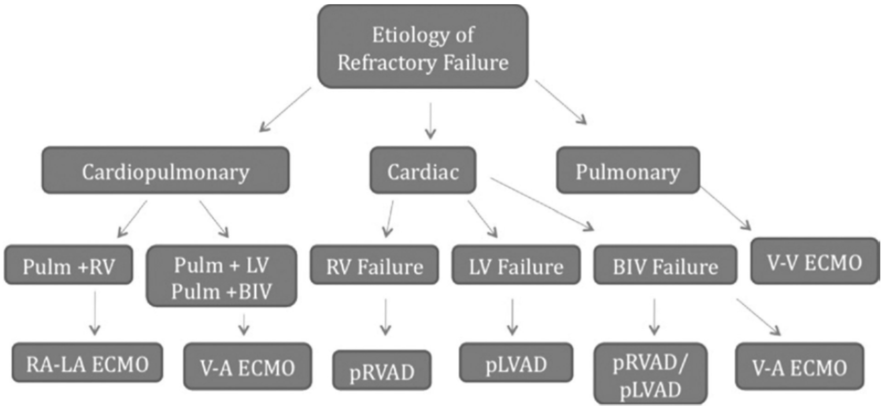
Options for RV failure

- TandemHeart RVAD / BiVAD
- Impella RP (investigational)
- Surgical (Centrimag) RVAD / BiVAD
- Veno-Venous ECMO (isolated RV failure)
- RA-LA ECMO (Pulmonary + RV failure)
- Veno-arterial ECMO (biventricular failure)



Kar, et al. Circulation 2012; 125: 1809-1817.

Selection of Percutaneous MCS for Refractory CS


Etiology of Refractory Failure

Cardiopulmonary

Cardiac

Pulmonary

Pulm +RV

Pulm + LV
Pulm +BIV

RV Failure

LV Failure

BIV Failure

V-V ECMO

RA-LA ECMO

V-A ECMO

pRVAD

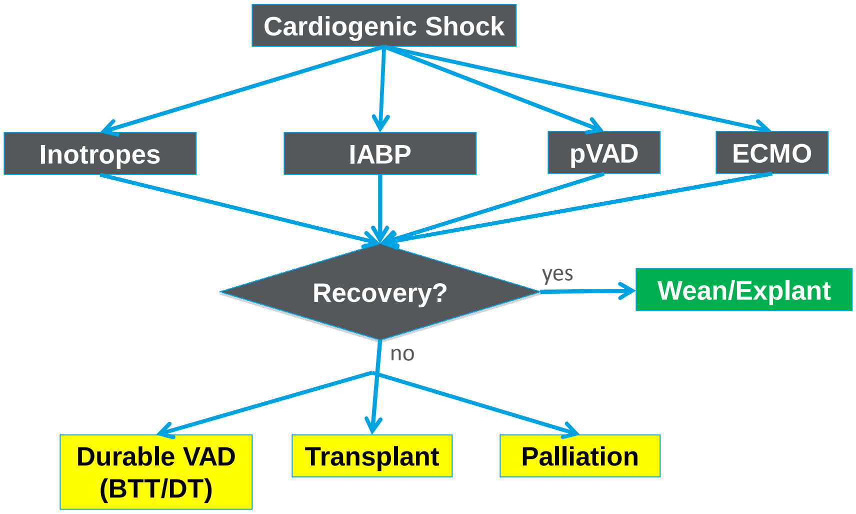
pLVAD

pRVAD/
pLVAD

V-A ECMO

Kar, et al. Circulation 2012; 125: 1809-1817.

Transitioning from Temporary MCS


Cardiogenic Shock
Inotropes
IABP
pVAD
ECMO
Recovery?
yes
Wean/Explant
no
Durable VAD (BTT/DT)
Transplant
Palliation

Expanding options for durable MCS

	HeartMate XVE	Thoratec IVAD*	HeartMate II	HeartWare HVAD	Jarvik 2000
Manufacturer	Thoratec	Thoratec	Thoratec	HeartWare	Jarvik Heart
Flow profile	Pulsatile	Pulsatile	Continuous (axial)	Continuous (centrifugal)	Continuous (axial)
Implant site	Abdomen	Abdomen	Abdomen	Pericardium	Pericardium
Driver	Electric	Pneumatic	Electric	Electric	Electric
Weight	1150 g	339 g	290 g	160 g	90 g
Displacement	400 mL	252 mL	63 mL	50 mL	25 mL
FDA approval	BTT, DT	BTT	BTT, DT	IDE	IDE

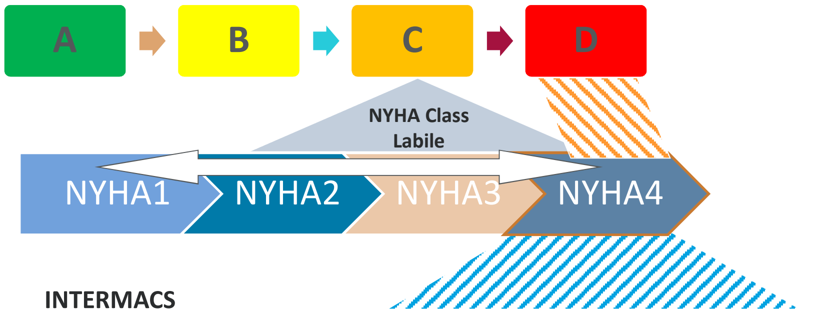
TAH

HeartMate 3

Stewart GC, Givertz MM. Circulation 2012; 125:1304-1315.

Patient Selection: The INTERMACS Profiles

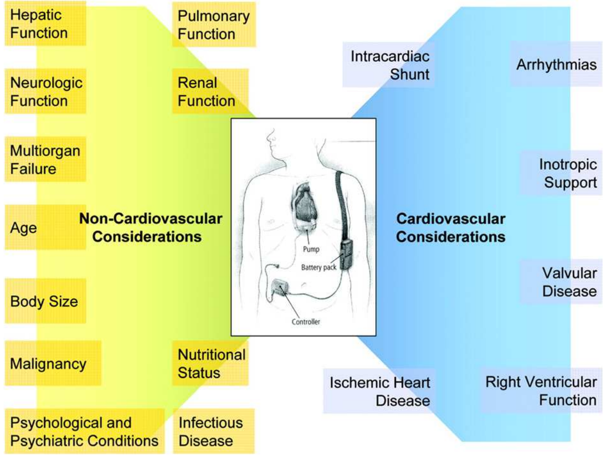
AHA/ACC Stages – one way only


A
B
C
D
NYHA Class
Labile
NYHA1
NYHA2
NYHA3
NYHA4
7
6
5
4
3
2
1

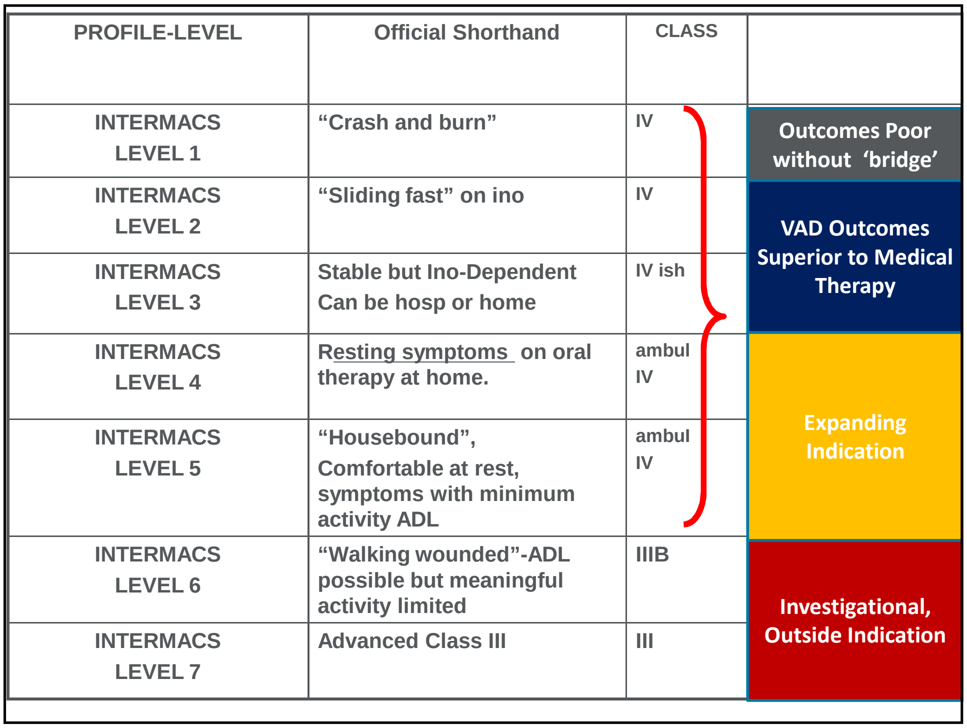
INTERMACS Profiles - Integrate Time

Stevenson LW, et al. JHLT 2009;28:535-41.
Liszkoswki M, et al. ISLHT Chicago 2010.

Candidacy for Long-Term MCS

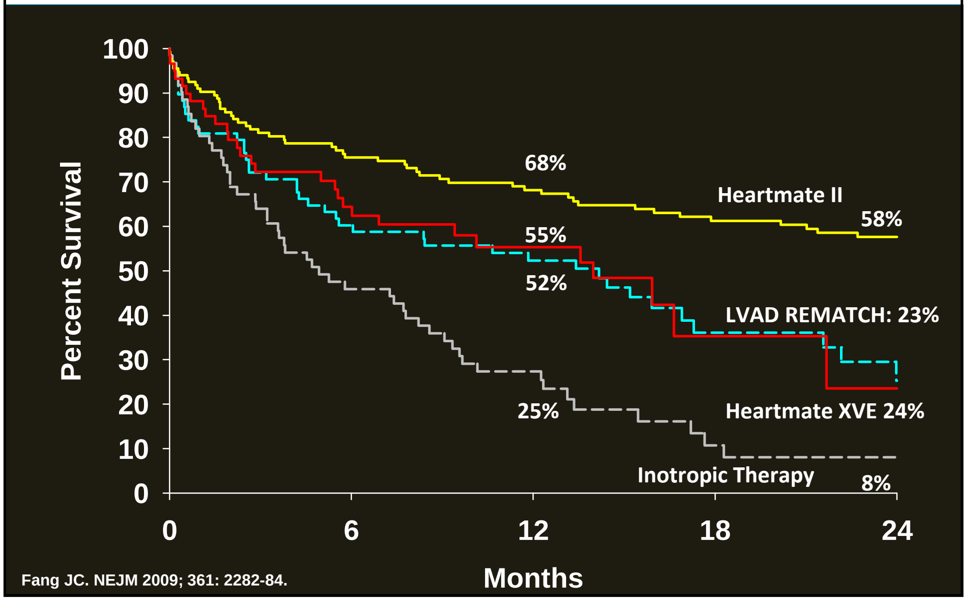

Hepatic Function
Pulmonary Function
Neurologic Function
Renal Function
Multiorgan Failure
Age
Non-Cardiovascular Considerations
Body Size
Malignancy
Nutritional Status
Psychological and Psychiatric Conditions
Infectious Disease
Pump
Battery pack
Controller
Intracardiac Shunt
Arrhythmias
Inotropic Support
Cardiovascular Considerations
Valvular Disease
Ischemic Heart Disease
Right Ventricular Function

Wilson et al. Circulation 2009;119:2225-2232

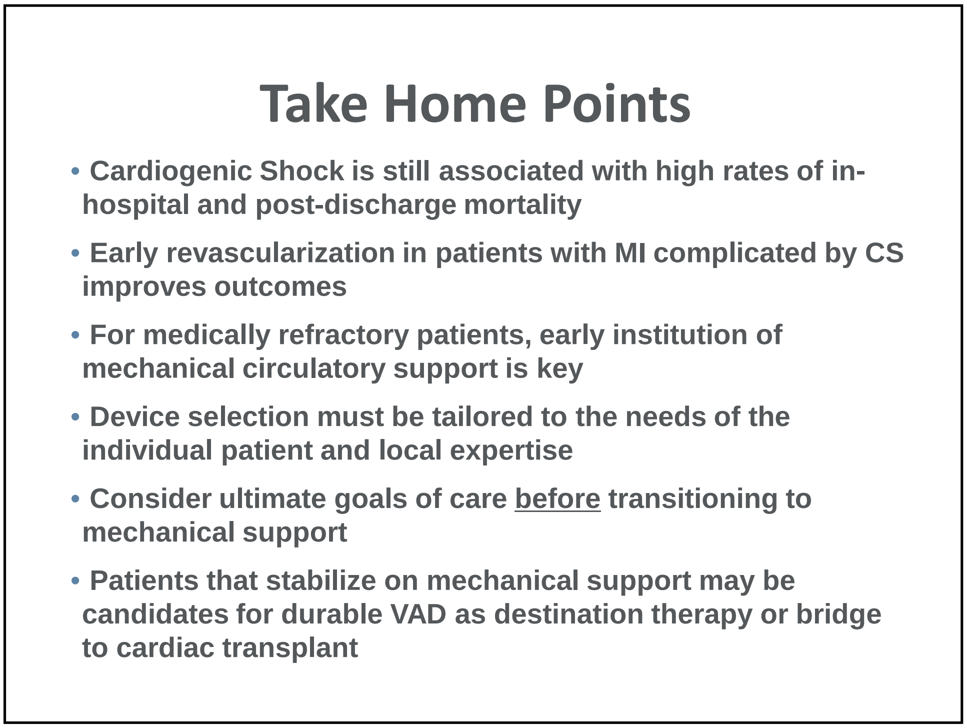


PROFILE-LEVEL	Official Shorthand	CLASS	
INTERMACS LEVEL 1	"Crash and burn"	IV	Outcomes Poor without 'bridge'
INTERMACS LEVEL 2	"Sliding fast" on ino	IV	VAD Outcomes Superior to Medical Therapy
INTERMACS LEVEL 3	Stable but Ino-Dependent Can be hosp or home	IV ish	
INTERMACS LEVEL 4	Resting symptoms on oral therapy at home.	ambul IV	Expanding Indication
INTERMACS LEVEL 5	"Housebound", Comfortable at rest, symptoms with minimum activity ADL	ambul IV	
INTERMACS LEVEL 6	"Walking wounded"-ADL possible but meaningful activity limited	IIIB	Investigational, Outside Indication
INTERMACS LEVEL 7	Advanced Class III	III	

Durable LVADs improve survival in Advanced HF

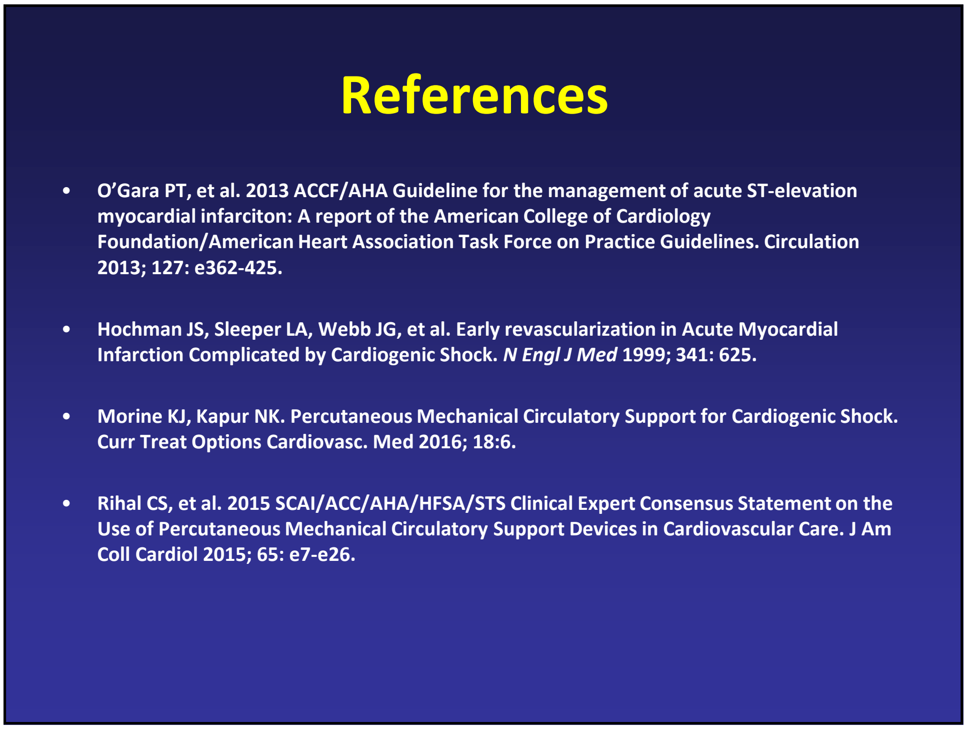


Fang JC. NEJM 2009; 361: 2282-84.



Take Home Points

- Cardiogenic Shock is still associated with high rates of in-hospital and post-discharge mortality
- Early revascularization in patients with MI complicated by CS improves outcomes
- For medically refractory patients, early institution of mechanical circulatory support is key
- Device selection must be tailored to the needs of the individual patient and local expertise
- Consider ultimate goals of care before transitioning to mechanical support
- Patients that stabilize on mechanical support may be candidates for durable VAD as destination therapy or bridge to cardiac transplant



References

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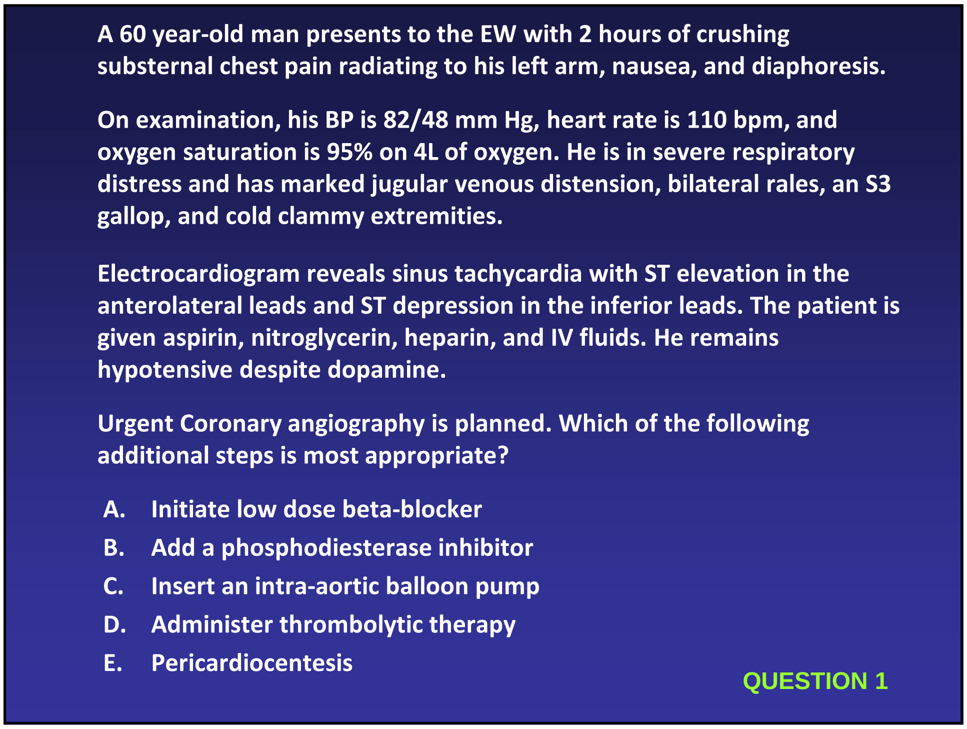
- Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in Acute Myocardial Infarction Complicated by Cardiogenic Shock. *N Engl J Med* 1999; 341: 625.
- Morine KJ, Kapur NK. Percutaneous Mechanical Circulatory Support for Cardiogenic Shock. Curr Treat Options Cardiovasc. Med 2016; 18:6.
- Rihal CS, et al. 2015 SCAI/ACC/AHA/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care. J Am Coll Cardiol 2015; 65: e7-e26.



A 60 year-old man presents to the EW with 2 hours of crushing substernal chest pain radiating to his left arm, nausea, and diaphoresis.

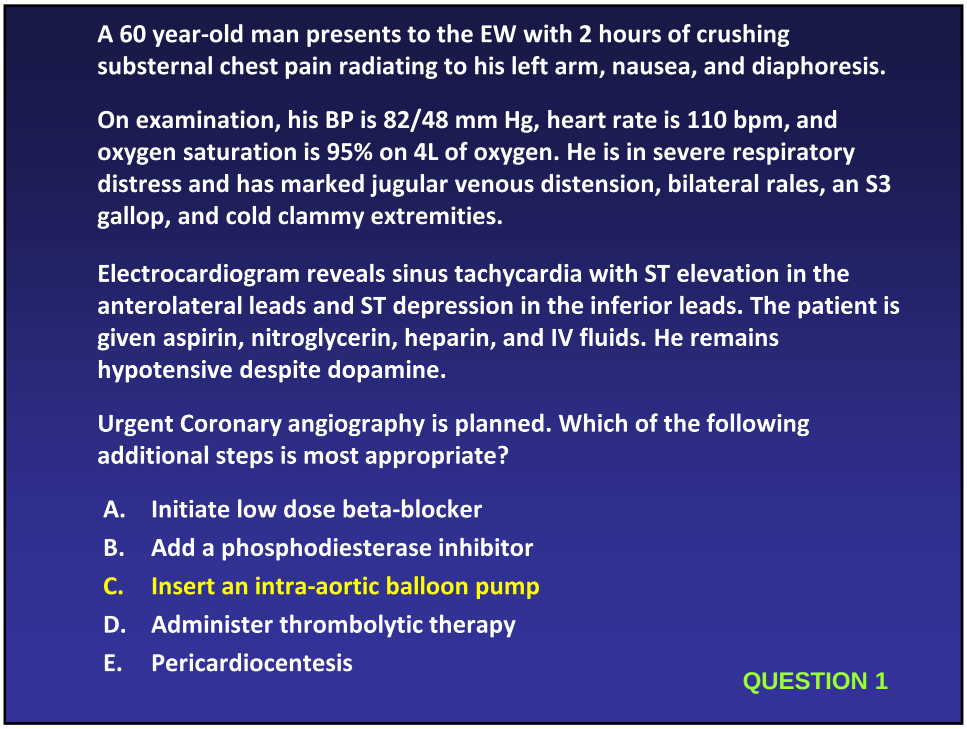
On examination, his BP is 82/48 mm Hg, heart rate is 110 bpm, and oxygen saturation is 95% on 4L of oxygen. He is in severe respiratory distress and has marked jugular venous distension, bilateral rales, an S3 gallop, and cold clammy extremities.

Electrocardiogram reveals sinus tachycardia with ST elevation in the anterolateral leads and ST depression in the inferior leads. The patient is given aspirin, nitroglycerin, heparin, and IV fluids. He remains hypotensive despite dopamine.

Urgent Coronary angiography is planned. Which of the following additional steps is most appropriate?

A. Initiate low dose beta-blocker
B. Add a phosphodiesterase inhibitor
C. Insert an intra-aortic balloon pump
D. Administer thrombolytic therapy
E. Pericardiocentesis

QUESTION 1



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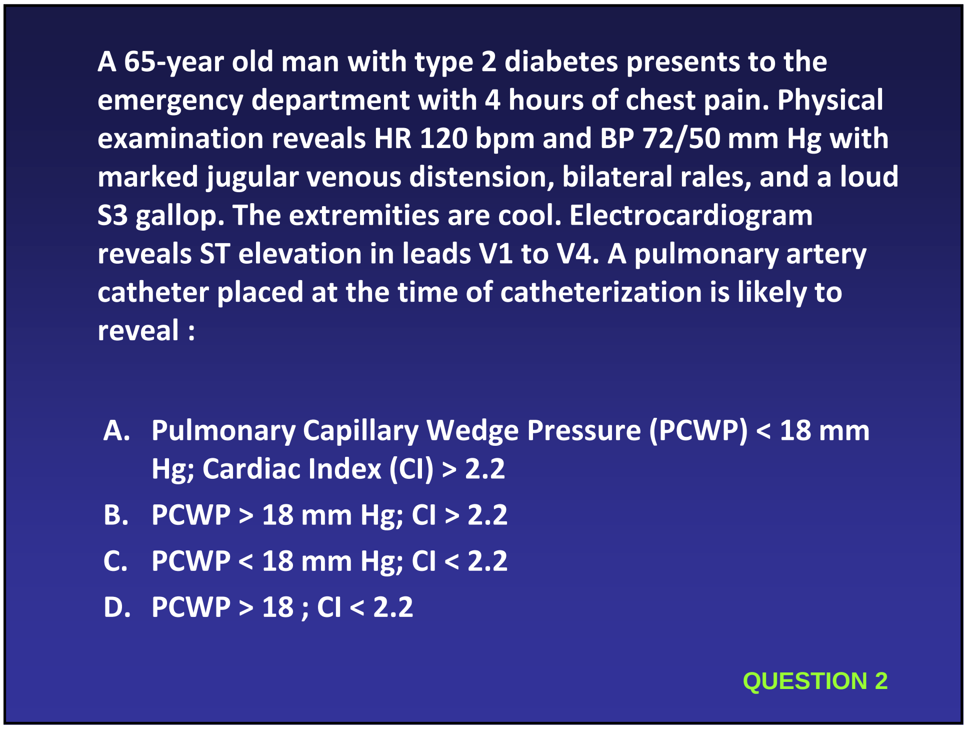
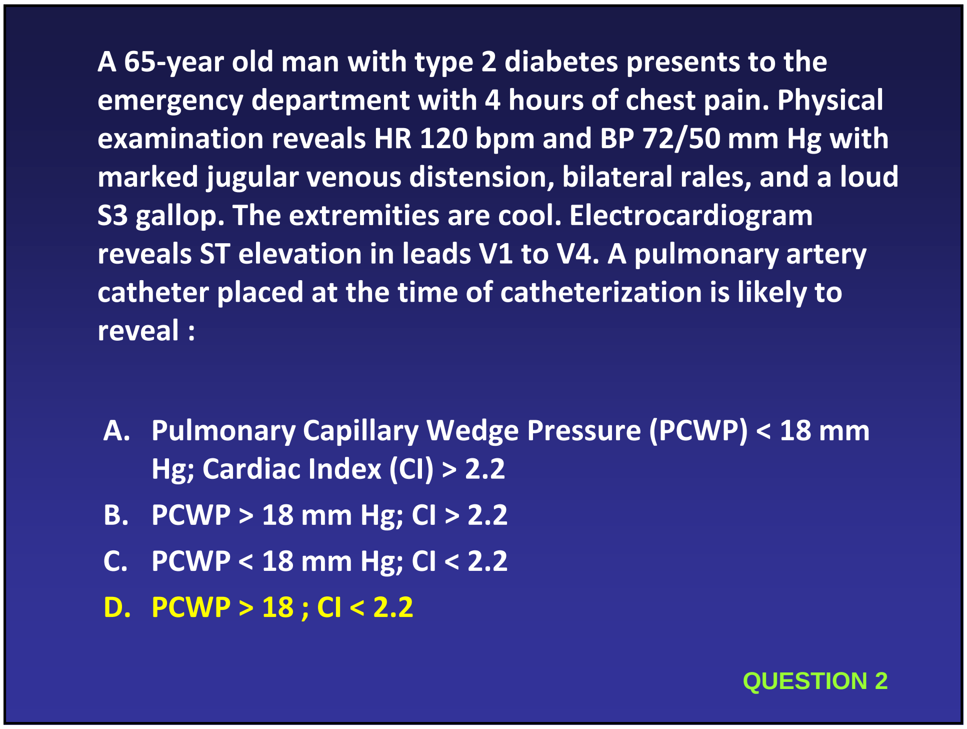


A 65-year old man with type 2 diabetes presents to the emergency department with 4 hours of chest pain. Physical examination reveals HR 120 bpm and BP 72/50 mm Hg with marked jugular venous distension, bilateral rales, and a loud S3 gallop. The extremities are cool. Electrocardiogram reveals ST elevation in leads V1 to V4. A pulmonary artery catheter placed at the time of catheterization is likely to reveal :

A. Pulmonary Capillary Wedge Pressure (PCWP) < 18 mm Hg; Cardiac Index (CI) > 2.2
B. PCWP > 18 mm Hg; CI > 2.2
C. PCWP < 18 mm Hg; CI < 2.2
D. PCWP > 18 ; CI < 2.2

QUESTION 2



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D. PCWP > 18 ; CI < 2.2

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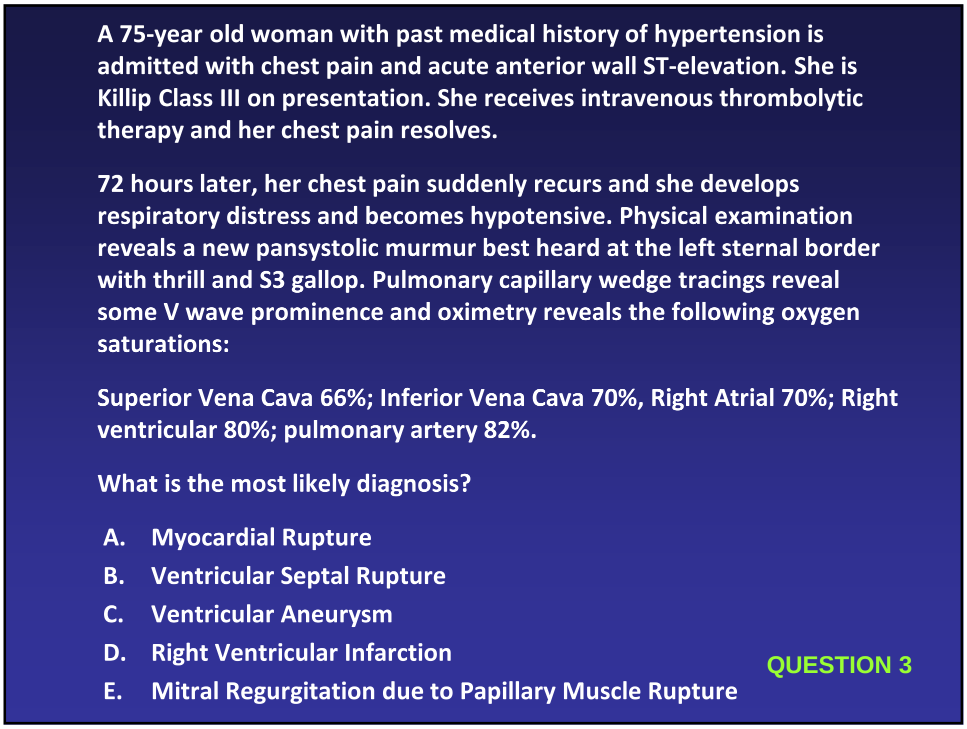


A 75-year old woman with past medical history of hypertension is admitted with chest pain and acute anterior wall ST-elevation. She is Killip Class III on presentation. She receives intravenous thrombolytic therapy and her chest pain resolves.

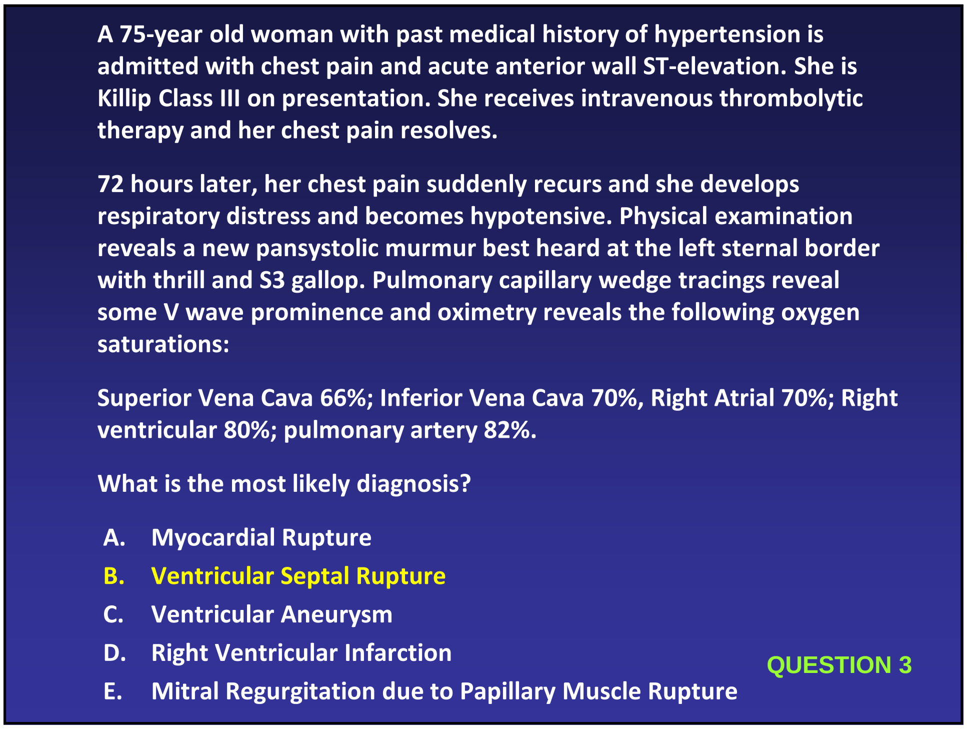
72 hours later, her chest pain suddenly recurs and she develops respiratory distress and becomes hypotensive. Physical examination reveals a new pansystolic murmur best heard at the left sternal border with thrill and S3 gallop. Pulmonary capillary wedge tracings reveal some V wave prominence and oximetry reveals the following oxygen saturations:

Superior Vena Cava 66%; Inferior Vena Cava 70%, Right Atrial 70%; Right ventricular 80%; pulmonary artery 82%.

What is the most likely diagnosis?

A. Myocardial Rupture
B. Ventricular Septal Rupture
C. Ventricular Aneurysm
D. Right Ventricular Infarction
E. Mitral Regurgitation due to Papillary Muscle Rupture

QUESTION 3



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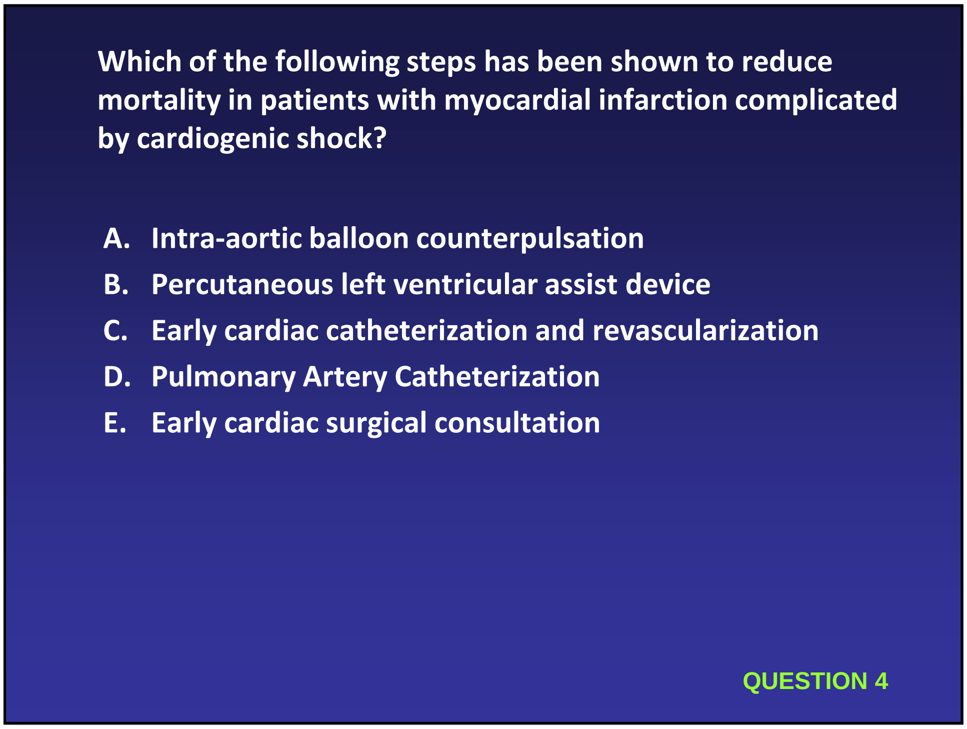
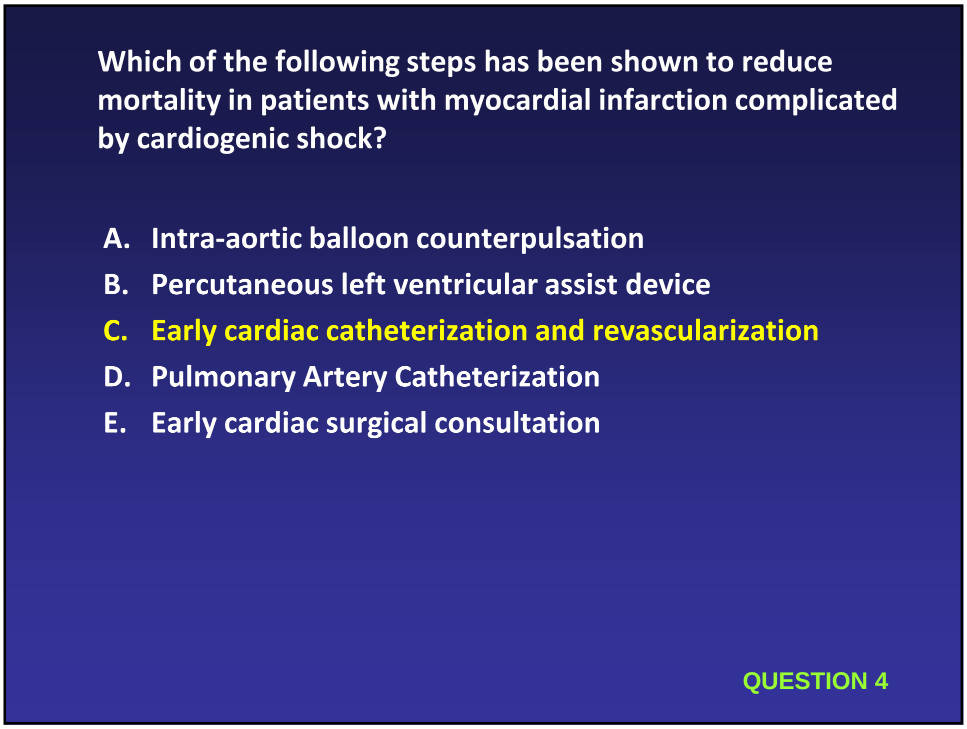


Which of the following steps has been shown to reduce mortality in patients with myocardial infarction complicated by cardiogenic shock?

A. Intra-aortic balloon counterpulsation
B. Percutaneous left ventricular assist device
C. Early cardiac catheterization and revascularization
D. Pulmonary Artery Catheterization
E. Early cardiac surgical consultation

QUESTION 4



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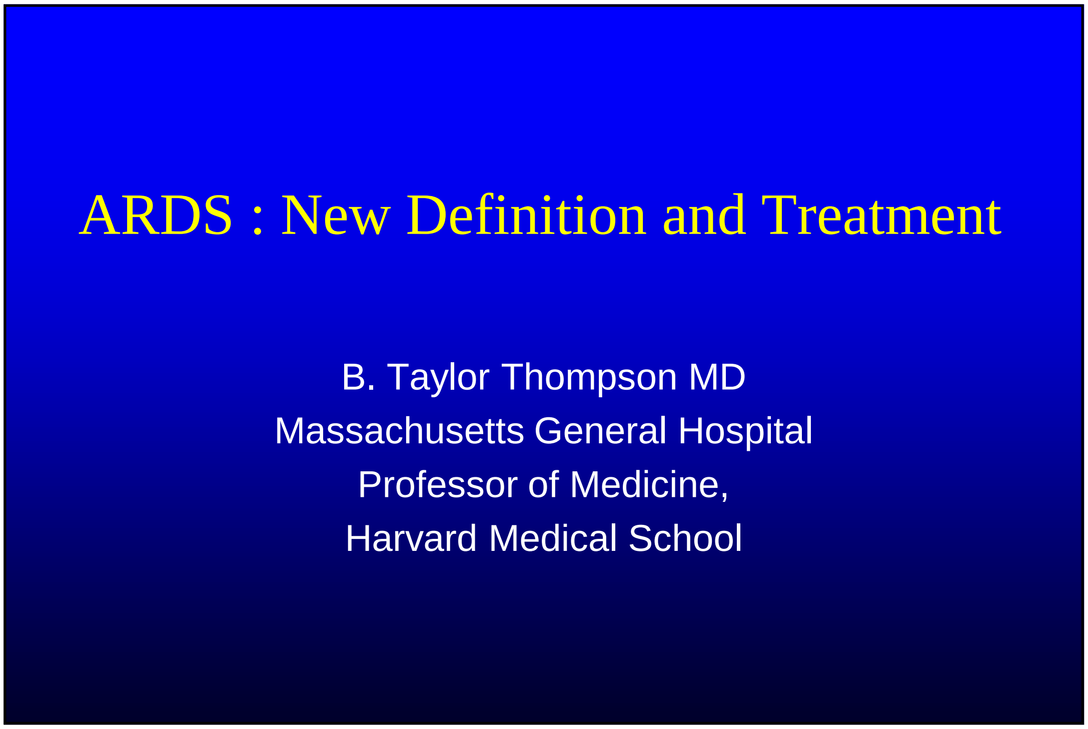
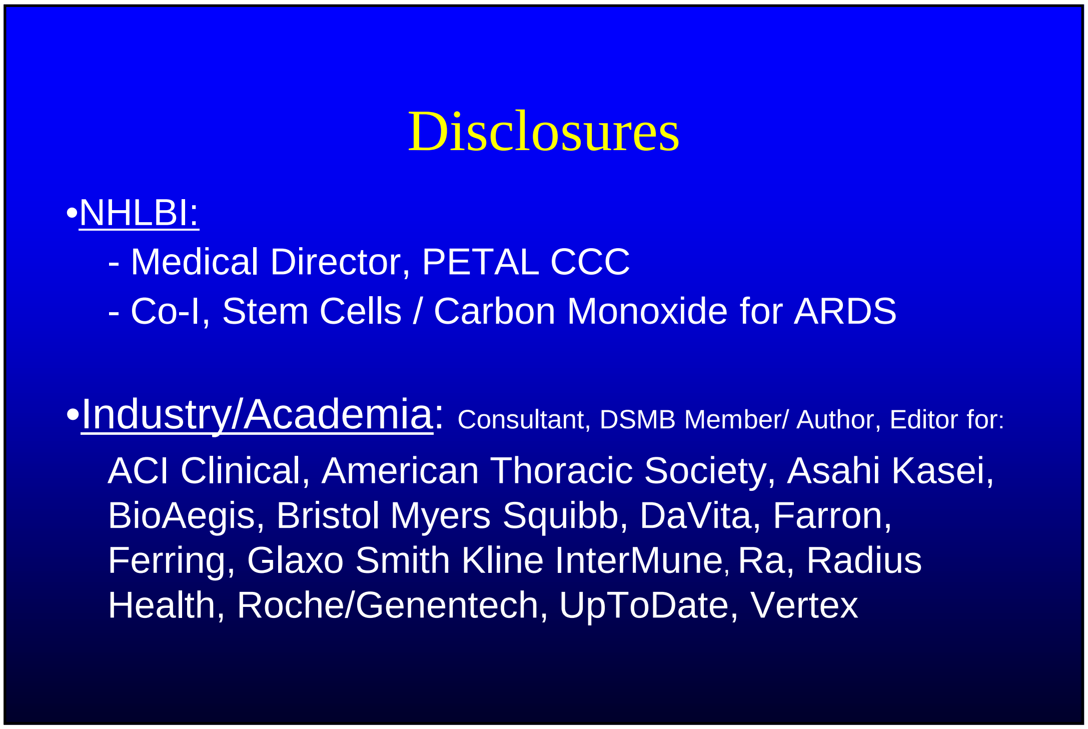
QUESTION 4



ARDS : New Definition and Treatment

B. Taylor Thompson MD
Massachusetts General Hospital
Professor of Medicine,
Harvard Medical School



Disclosures

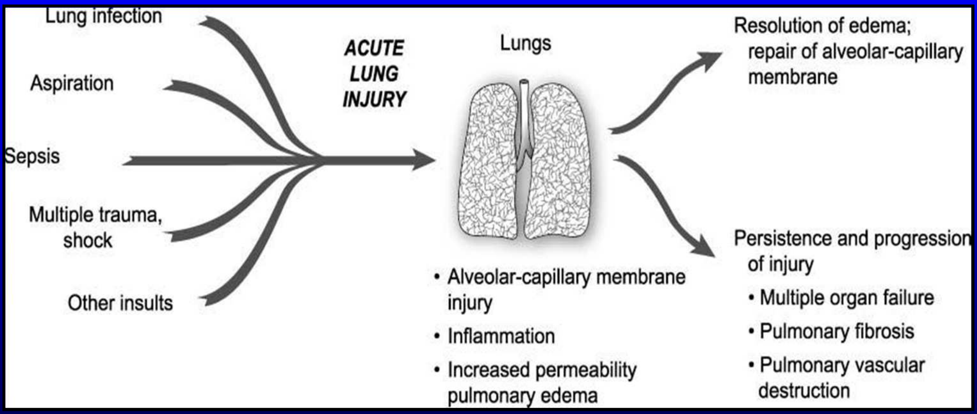
- NHLBI:
  - Medical Director, PETAL CCC
  - Co-I, Stem Cells / Carbon Monoxide for ARDS

- Industry/Academia: Consultant, DSMB Member/ Author, Editor for:
  ACI Clinical, American Thoracic Society, Asahi Kasei, BioAegis, Bristol Myers Squibb, DaVita, Farron, Ferring, Glaxo Smith Kline InterMune, Ra, Radius Health, Roche/Genentech, UpToDate, Vertex

ARDS I: Outline

- The Berlin Definition of ARDS
  - – ARDS can be multi-focal on CXR
  - – May coexist with heart failure
- Pharmacologic Therapy

ARDS


Lung infection
Aspiration
Sepsis
Multiple trauma, shock
Other insults
ACUTE LUNG INJURY
Lungs
• Alveolar-capillary membrane injury
• Inflammation
• Increased permeability pulmonary edema
Resolution of edema; repair of alveolar-capillary membrane
Persistence and progression of injury
• Multiple organ failure
• Pulmonary fibrosis
• Pulmonary vascular destruction

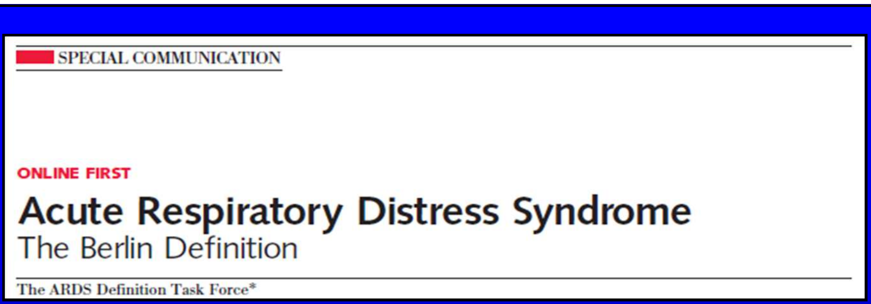
Matthay et al. AJRCMB 2005

ALI/ARDS in the United States in 2000

Estimates

- 190,600 ALI/ARDS cases per year
- 74,500 deaths
- 3.6 million hospital days
- *Pneumonia or septic shock* as the ALI risk factor in ~80%

Rubenfeld et al *NEJM* 2005



SPECIAL COMMUNICATION

ONLINE FIRST

Acute Respiratory Distress Syndrome

The Berlin Definition

The ARDS Definition Task Force*

CHAIRS:

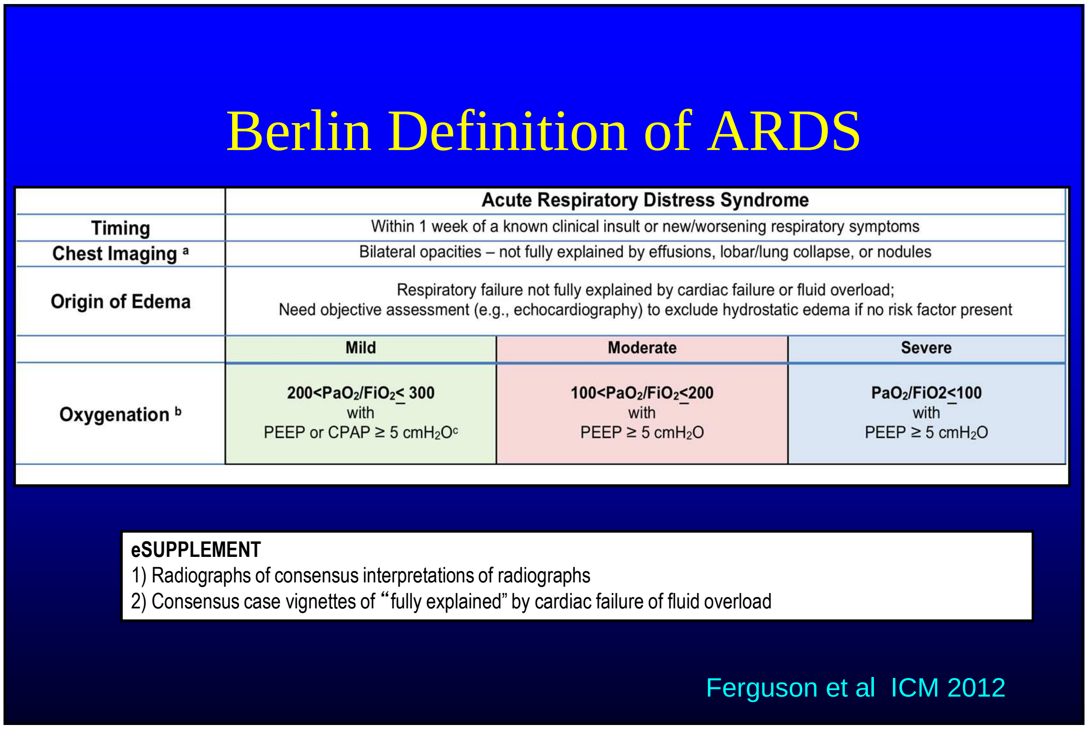
Marco Ranieri, Gordon Rubenfeld MD, Taylor Thompson

EUROPE

M. Antonelli, R. Beale, L. Brochard, L. Gattinoni, A. Esteban, JL Vincent, A. Rhodes

US/CANADA

A. Anzueto, R. Brower, N. Fergusson, A. Slutsky

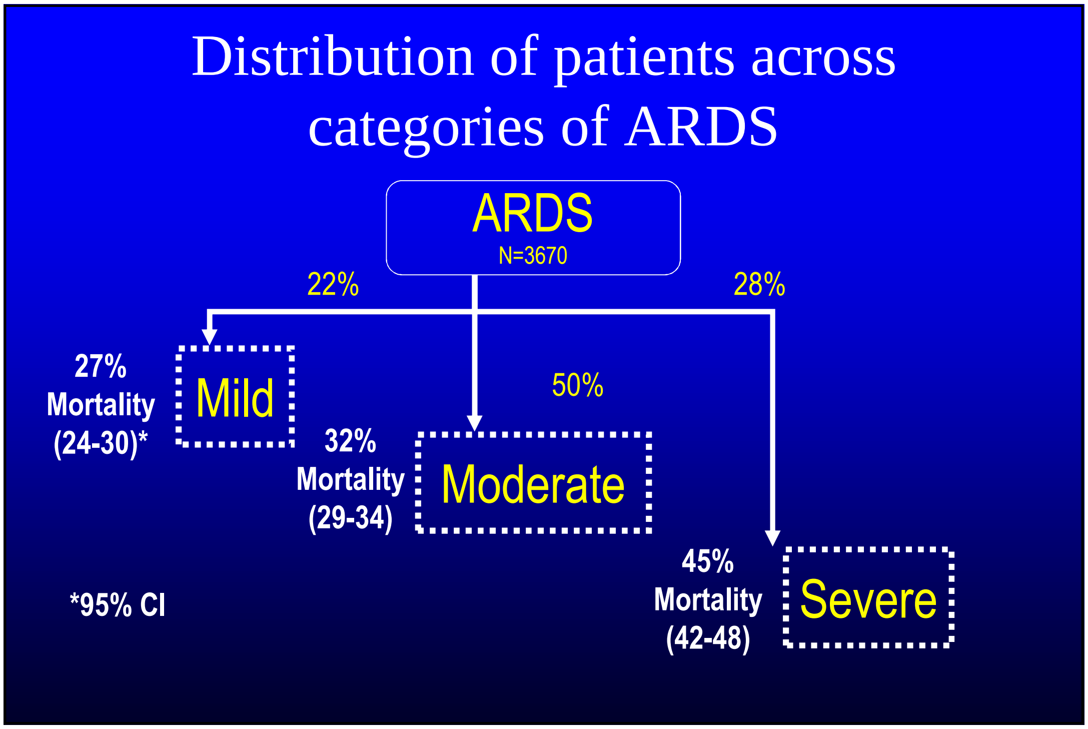


Berlin Definition of ARDS

	Acute Respiratory Distress Syndrome		
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Chest Imaging [a]	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present		
	Mild	**Moderate**	**Severe**
Oxygenation [b]	**$200<PaO_2/FiO_2\leq 300$** with PEEP or CPAP ≥ 5 cmH_2O[c]	**$100<PaO_2/FiO_2\leq 200$** with PEEP ≥ 5 cmH_2O	**$PaO_2/FiO2\leq 100$** with PEEP ≥ 5 cmH_2O

eSUPPLEMENT
1) Radiographs of consensus interpretations of radiographs
2) Consensus case vignettes of "fully explained" by cardiac failure of fluid overload

Ferguson et al ICM 2012



Distribution of patients across categories of ARDS

ARDS
N=3670

22%

28%

50%

27%
Mortality
(24-30)*

Mild

32%
Mortality
(29-34)

Moderate

45%
Mortality
(42-48)

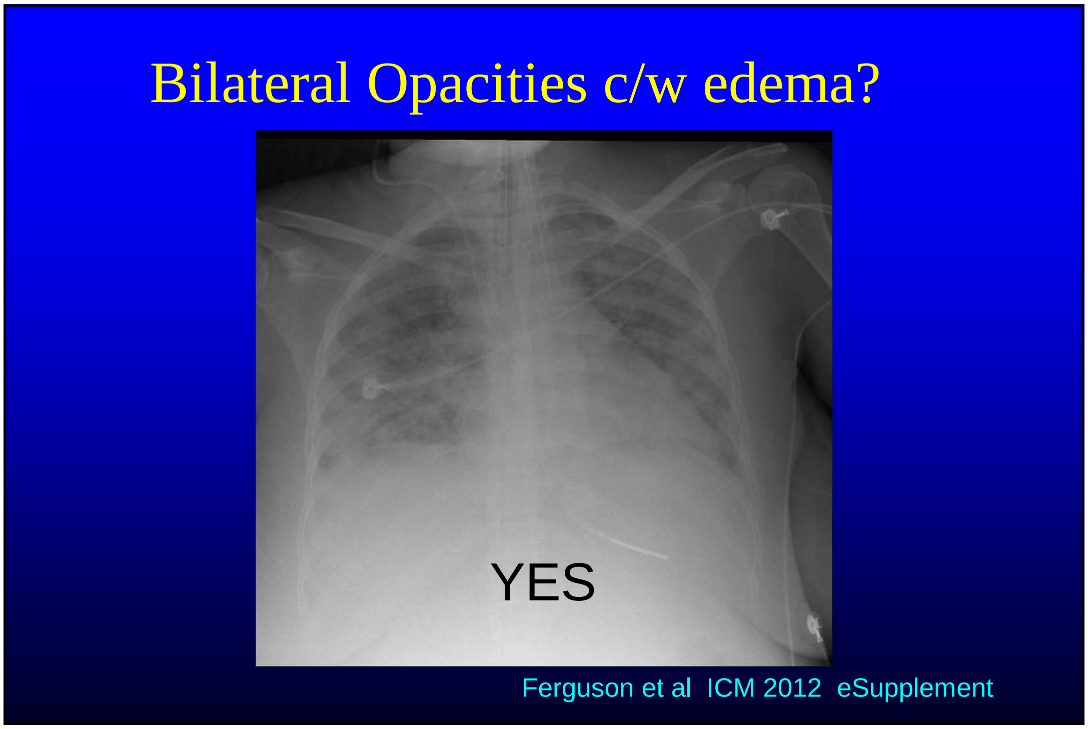
Severe

*95% CI

Berlin CXR Definitions/Refinements

- Bilateral opacities *consistent with pulmonary edema* may be very mild, patchy, and asymmetric. Opacities should not be fully explained by pleural effusions, pulmonary nodules or masses, or lobar/lung collapse
- 12 chest x-rays published as examples of opacities that are consistent with pulmonary edema (or not)

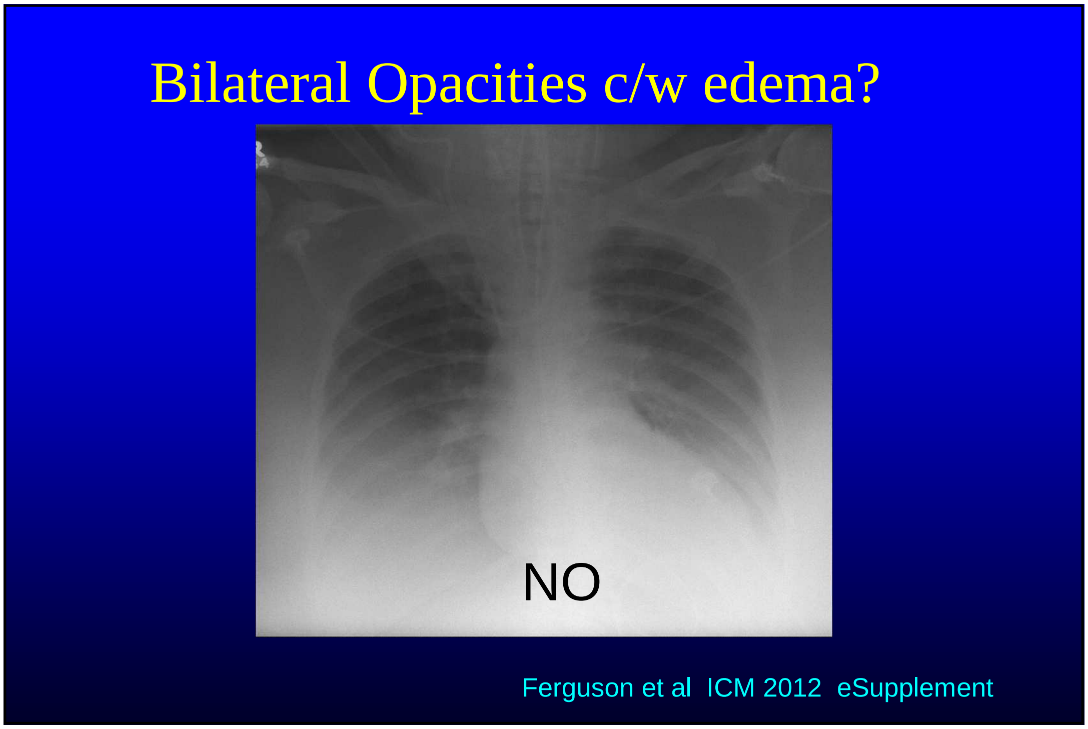
Ferguson et al ICM 2012 eSupplement



Bilateral Opacities c/w edema?

YES

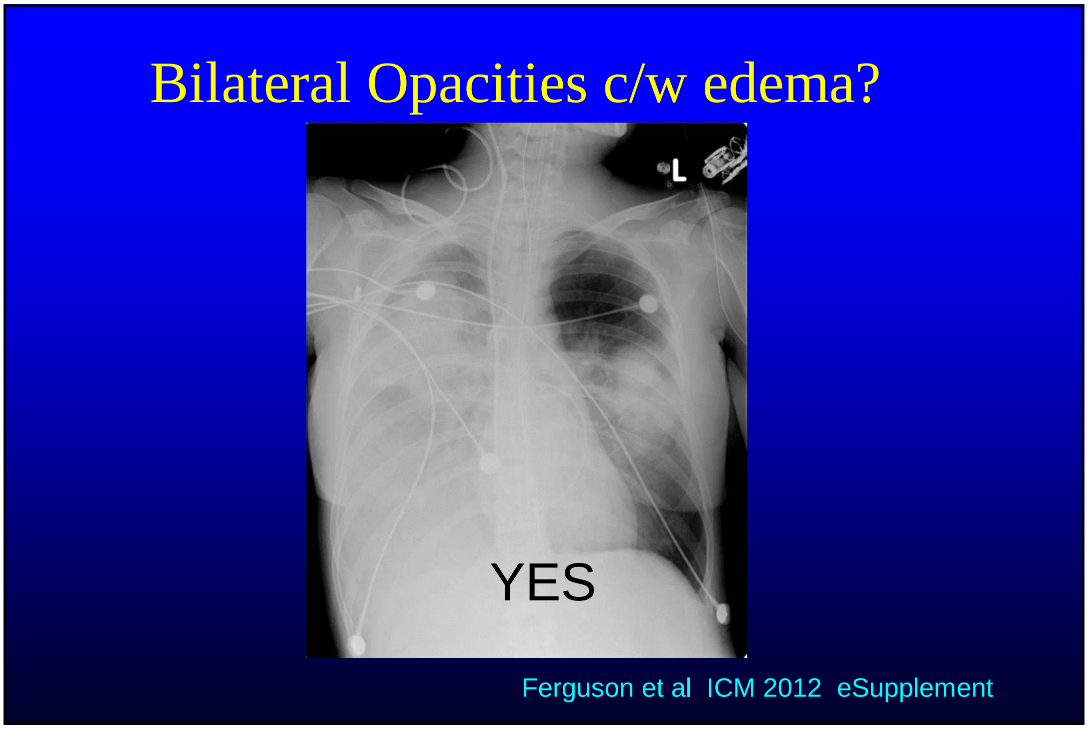
Ferguson et al ICM 2012 eSupplement



Bilateral Opacities c/w edema?

NO

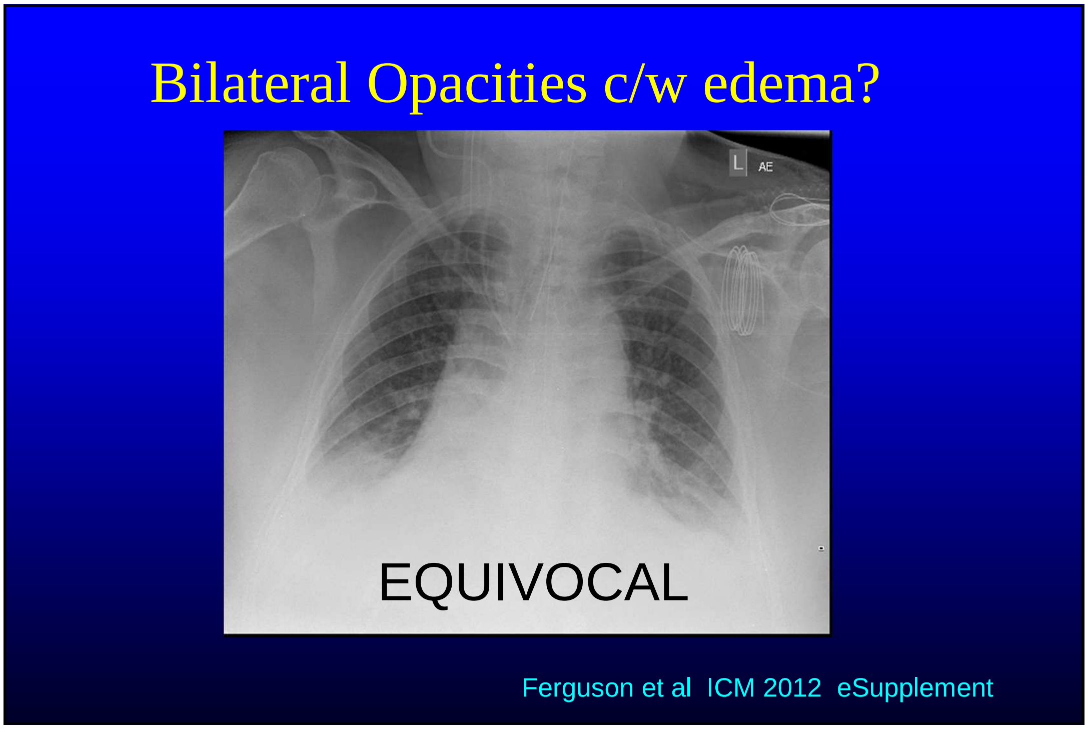
Ferguson et al ICM 2012 eSupplement



Bilateral Opacities c/w edema?

YES

Ferguson et al ICM 2012 eSupplement



Bilateral Opacities c/w edema?

EQUIVOCAL

Ferguson et al ICM 2012 eSupplement

Berlin Definition: assessment of LAH

- The Berlin ARDS definition shifts the focus from excluding patients with left atrial hypertension to excluding patients with only left atrial hypertension as an explanation for their clinical syndrome. Why?
  - ARDS and left atrial hypertension frequently co-exist
  - Left ventricular dysfunction is common in patients with sepsis
  - The chest radiograph, BNP, and troponin cannot distinguish CHF from ARDS

Ferguson et al ICM 2012 eSupplement

Berlin Definition: assessment of LAH

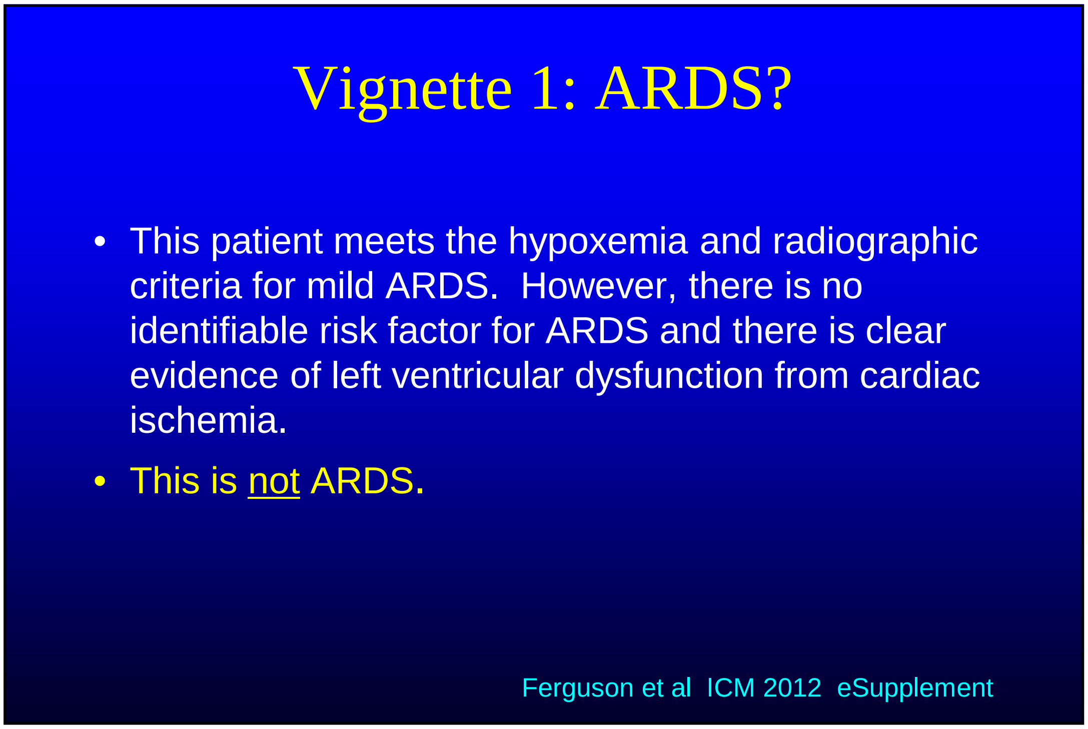
- Patients with a clinical syndrome compatible with ARDS are likely to present on a spectrum from clear cardiogenic edema to clear ARDS, with many cases existing in the middle.
- Vignettes are meant to illustrate this spectrum and guide clinicians in their thinking about similar cases.

Ferguson et al ICM 2012 eSupplement

Vignette 1

- A 53 y/o man presents to the ED with substernal chest pain and dyspnea of 2 hours duration. He is afebrile and tachypneic, with bilateral rales. The SpO_2 on 100% oxygen face mask is 96%. The EKG shows antero-lateral ischemia and the CXR demonstrates pulmonary edema. A rapid troponin T assay is 0.10 ug/L (upper limit of normal 0.03 ug/L). An emergent echocardiogram shows decreased left ventricular function with focal wall motion abnormality. An attempt at non-invasive ventilation fails as the patient becomes hemodynamically unstable. After intubation, the PaO_2/FiO_2 ratio on FiO_2 0.60 is 230.

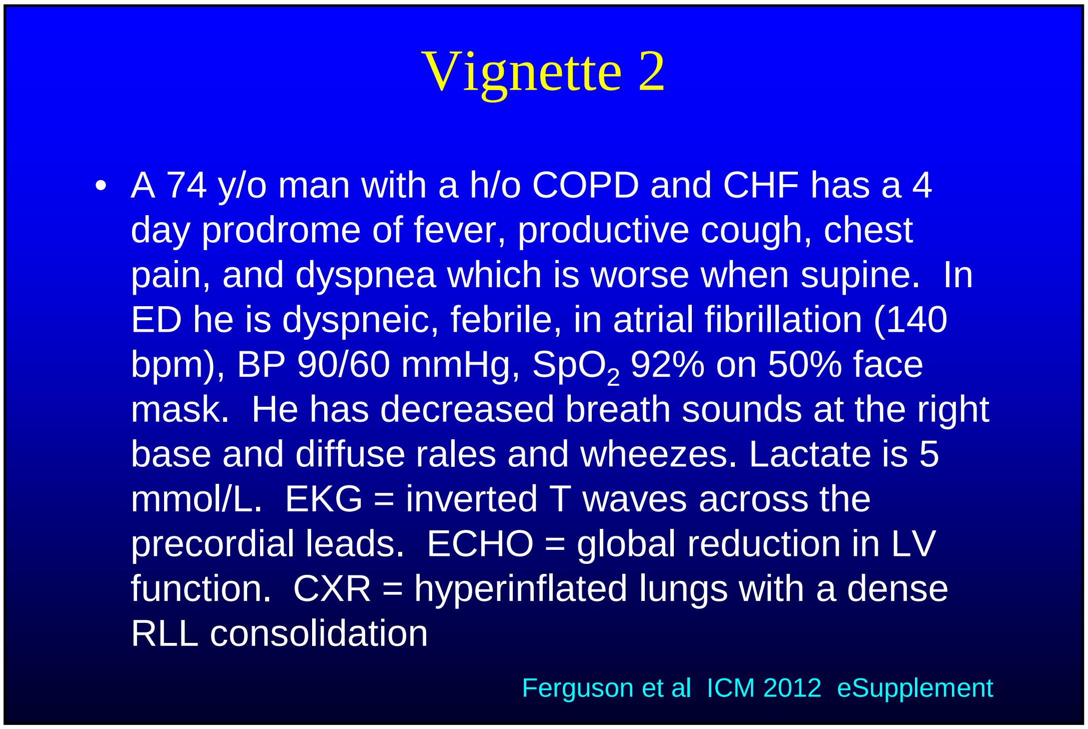
Ferguson et al ICM 2012 eSupplement



Vignette 1: ARDS?

- This patient meets the hypoxemia and radiographic criteria for mild ARDS. However, there is no identifiable risk factor for ARDS and there is clear evidence of left ventricular dysfunction from cardiac ischemia.
- This is not ARDS.

Ferguson et al ICM 2012 eSupplement



Vignette 2

- A 74 y/o man with a h/o COPD and CHF has a 4 day prodrome of fever, productive cough, chest pain, and dyspnea which is worse when supine. In ED he is dyspneic, febrile, in atrial fibrillation (140 bpm), BP 90/60 mmHg, SpO_2 92% on 50% face mask. He has decreased breath sounds at the right base and diffuse rales and wheezes. Lactate is 5 mmol/L. EKG = inverted T waves across the precordial leads. ECHO = global reduction in LV function. CXR = hyperinflated lungs with a dense RLL consolidation

Ferguson et al ICM 2012 eSupplement

Vignette 2 (cont)

- Two liters of NS -> transient increase in BP but requires intubation and norepi. CXR shows the RLL opacity, a right pleural effusion, and evolving left sided infiltrates.
- The CVP is 15 mmHg and an $ScvO_2$ of 55%. ABG post intubation reveals a PaO_2/FiO_2 ratio of 180 on FiO2 0.6. The troponin T is 0.06 ug/L.

Ferguson et al ICM 2012 eSupplement

Vignette 2: ARDS?

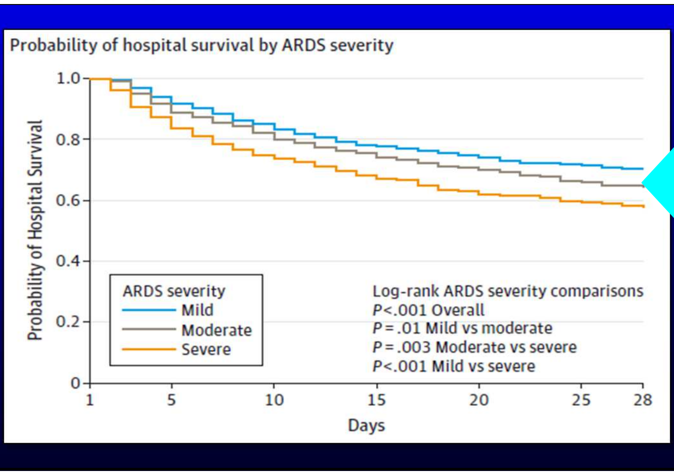
- This case is a common scenario. The patient meets oxygenation and radiographic criteria for moderate ARDS. Clearly, the patient has pneumonia and likely has pre-existing left ventricular dysfunction. Troponin elevations are common in patients with septic shock. The evolution of bilateral opacities might indicate a degree of left atrial hypertension, *but this does not exclude a diagnosis of ARDS.*
- This is ARDS; probably with a component of hydrostatic edema.

Ferguson et al ICM 2012 eSupplement

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tài Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MASc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group



51-79% of cases unrecognized by clinicians as "ARDS"

JAMA 2016

Diagnostic or Prognostic Biomarkers: no "troponin of the lung"

- **Inflammation** - IL-6, IL-8, sTNFRI, CRP
- **Disordered Coagulation** - Protein C, PAI-1
- **Endothelial injury** - Von Willebrand factor antigen
- **Myocardial Injury** – Troponin, BNP
- **Alveolar epithelium** - SP-D, sTNFRI, & RAGE
- **Adhesion molecule** - sICAM-1
- **Fibroblast proliferation** - PCPIII
- **Elastin breakdown product** - Desmosine (urine)
- **Nitric Oxide Levels** – exhaled NO

Ware , CCM 2014; Calfee, Lancet Resp Med 2014

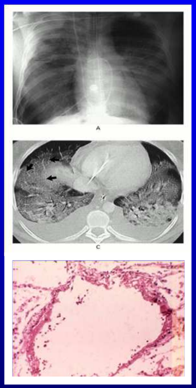
ARDS I: Outline

- The Berlin Definition of ARDS
  - ARDS can be multi-focal on CXR
  - May coexist with heart failure
- Pharmacologic Therapy

Drug Trials for ARDS

Early ARDS

- ~~nitric oxide~~
- ~~surfactant/perflourocarbon~~
- ~~prostaglandin E1~~
- ~~lysophylline~~
- ~~ibuprofen~~
- ~~procysteine~~
- ~~anticytokine/antiendotoxin~~
- ~~ketoconazole~~
- ~~Heparin/streptokinase~~
- ~~neutrophil elastase inhibitor~~
- ~~sPLA$_2$ inhibitor~~
- ~~rhAPC~~
- ~~Albuterol/salmeterol~~
- corticosteroids
- furosemide
- cisatricurium



Drug Trials for ARDS

Early ARDS

- ~~nitric oxide~~
- ~~surfactant/perflourocarbon~~
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- ~~lysophylline~~
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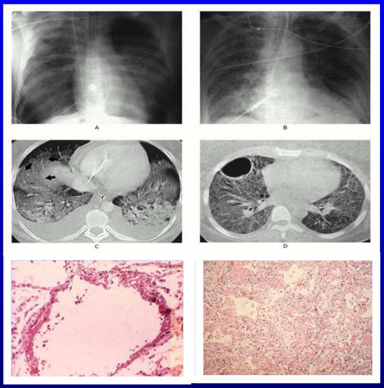
- ~~neutrophil elastase inhibitor~~
- ~~$sPLA_2$ inhibitor~~
- ~~rhAPC~~
- ~~Albuterol/salmeterol~~
- corticosteroids
- furosemide
- cisatricurium

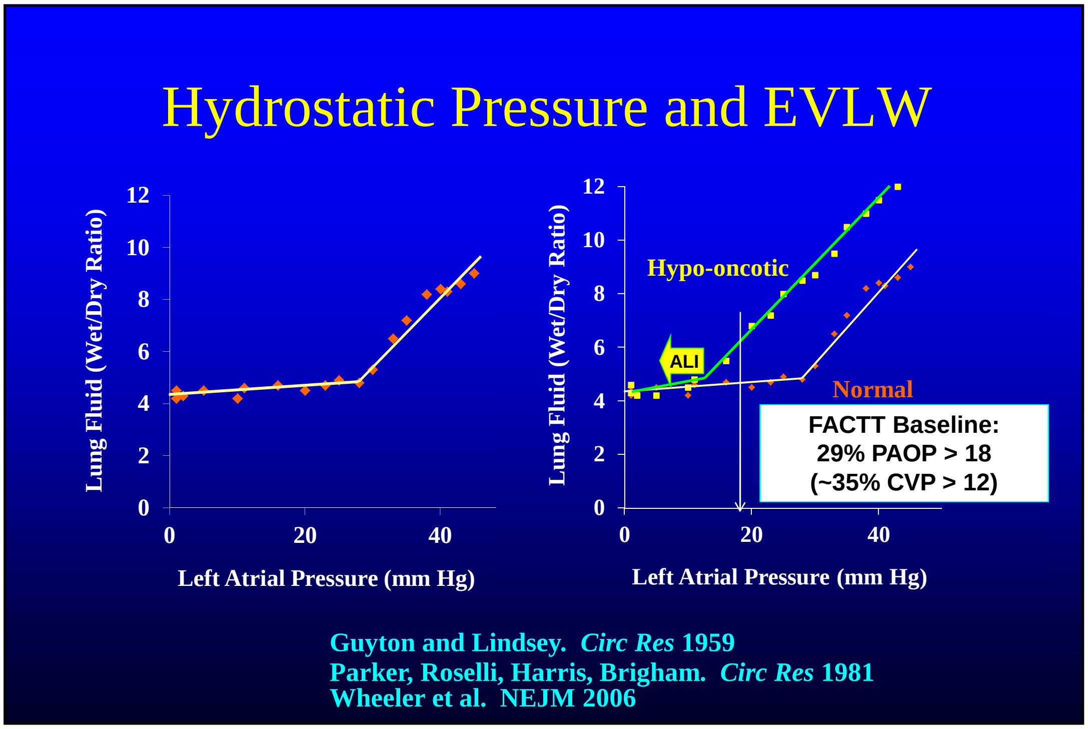


Late ARDS

- corticosteroids ?
- GMCSF?

ARDS Pharmacologic Rx

- Furosemide
- Cisatricurium
- Corticocosteroids



Hydrostatic Pressure and EVLW

FACTT Baseline:
29% PAOP > 18
(~35% CVP > 12)

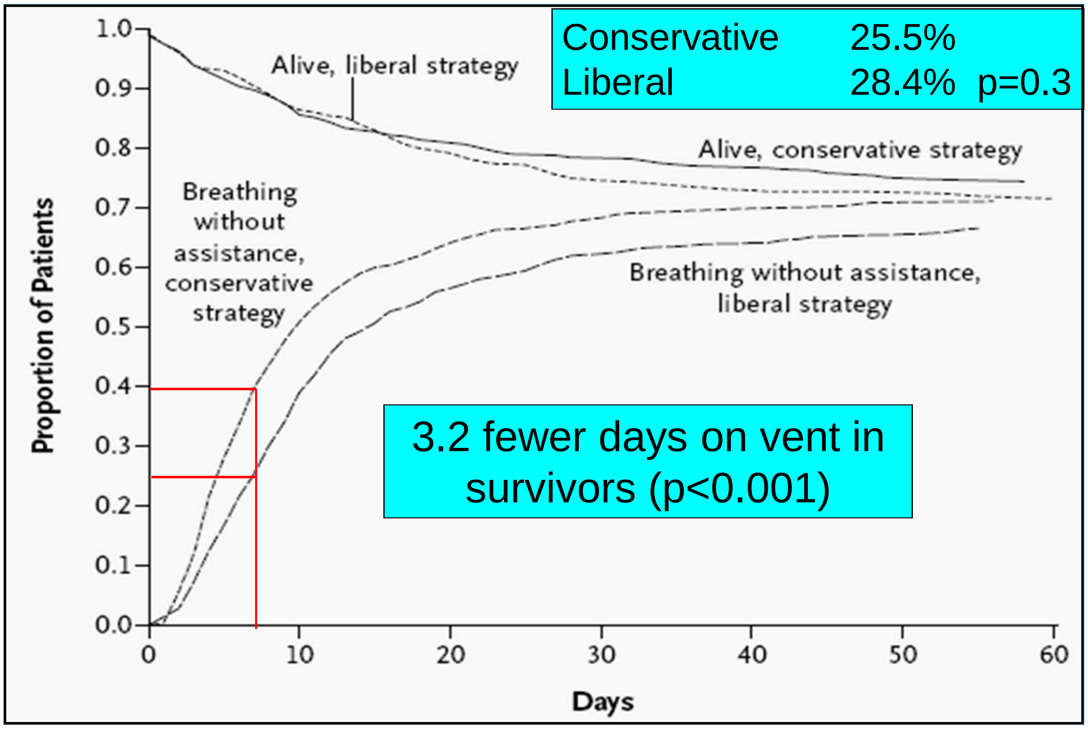
Guyton and Lindsey. *Circ Res* 1959
Parker, Roselli, Harris, Brigham. *Circ Res* 1981
Wheeler et al. NEJM 2006

FACTT: Protocol for Deresuscitation

- When shock-free:
  - No maintenance fluids
  - Diuretics to *normalize* CVP until off-vent, as tolerated
  - Hold diuretic for rising creatinine and/or active urine sediment

FACTT Fluid: Safety

- Conservative Fluid (Active Deresuscitation)
  - More adverse events of hypokalemia and metabolic alkalosis
- No difference
  - New shock (~15% in each arm) or shock duration
  - Renal failure
  - Renal Replacement Therapy
    - 10% in conservative vs 14% in liberal (p=0.06)

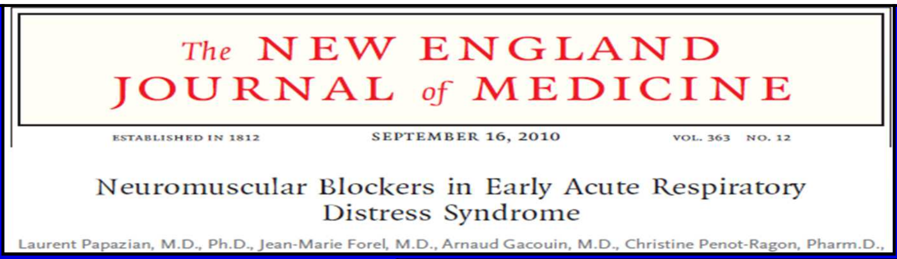


Conservative	25.5%	
Liberal	28.4%	p=0.3

3.2 fewer days on vent in survivors (p<0.001)

ARDS Pharmacologic Rx

- Furosemide
- ➡ Cisatricurium
- Corticocosteroids



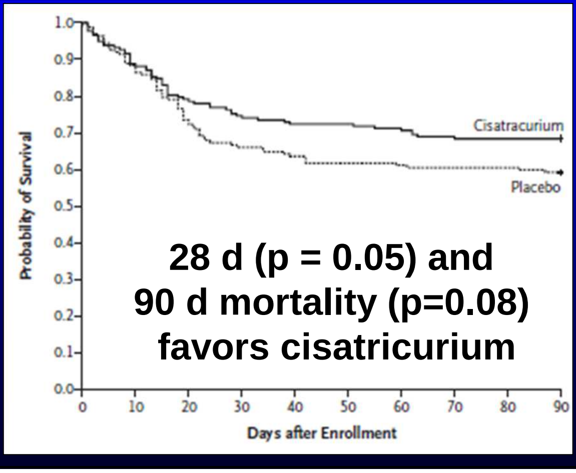
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

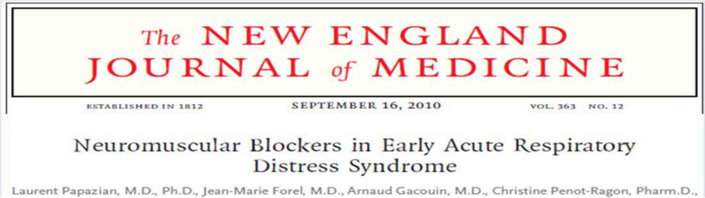
Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D.,

- N = 340 subjects with P/F < 150
- Vt 6-8 ml/kg. deep sedation
- Randomized 1:1 to the addition of cisatricurium x 48 hrs (15 mg bolus, 37.5 mg/hr)



28 d (p = 0.05) and 90 d mortality (p=0.08) favors cisatricurium



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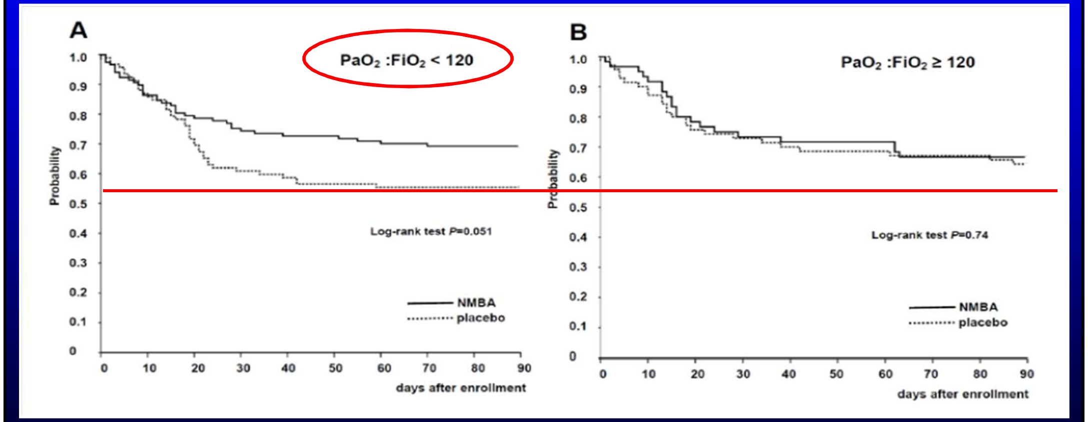
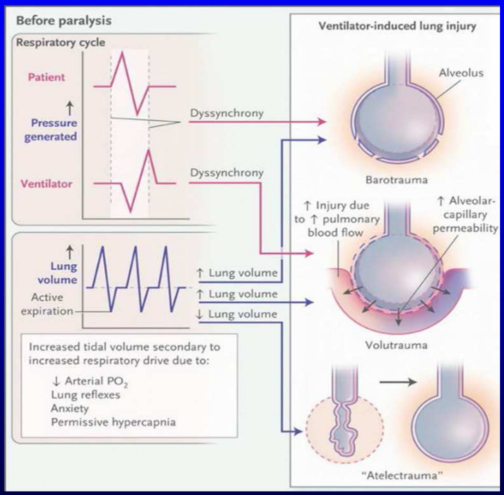
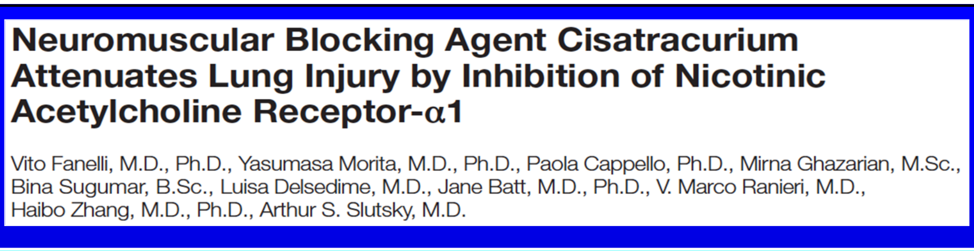


Potential Role of Neuromuscular Blockade in ARDS

- Improve patient-ventilator interface
    - Reduce volutrauma
    - Reduce atelectrauma
    - Reduce VILI
- Reduce respiratory muscle O_2 consumption
    - Reduce cardiac output
    - Decrease pulmonary blood flow
    - Decrease alveolar fluid accumulation


Before paralysis
Respiratory cycle
Patient
Pressure generated
Ventilator
Dyssynchrony
Dyssynchrony
Lung volume
Active expiration
↑ Lung volume
↑ Lung volume
↓ Lung volume
Increased tidal volume secondary to increased respiratory drive due to:
↓ Arterial PO2
Lung reflexes
Anxiety
Permissive hypercapnia
Ventilator-induced lung injury
Alveolus
Barotrauma
↑ Injury due to ↑ pulmonary blood flow
↑ Alveolar-capillary permeability
Volutrauma
"Atelectrauma"

Slutsky NEJM 2010



Neuromuscular Blocking Agent Cisatracurium Attenuates Lung Injury by Inhibition of Nicotinic Acetylcholine Receptor-$\alpha 1$

Vito Fanelli, M.D., Ph.D., Yasumasa Morita, M.D., Ph.D., Paola Cappello, Ph.D., Mirna Ghazarian, M.Sc., Bina Sugumar, B.Sc., Luisa Delsedime, M.D., Jane Batt, M.D., Ph.D., V. Marco Ranieri, M.D., Haibo Zhang, M.D., Ph.D., Arthur S. Slutsky, M.D.

If cisatracurium improves ARDS outcomes via anti-inflammatory effects, standard dosing (for neuromuscular block) may be suboptimal for this effect

acetylcholine receptor α1 expression

ANESTHESIOLOGY 2016

PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

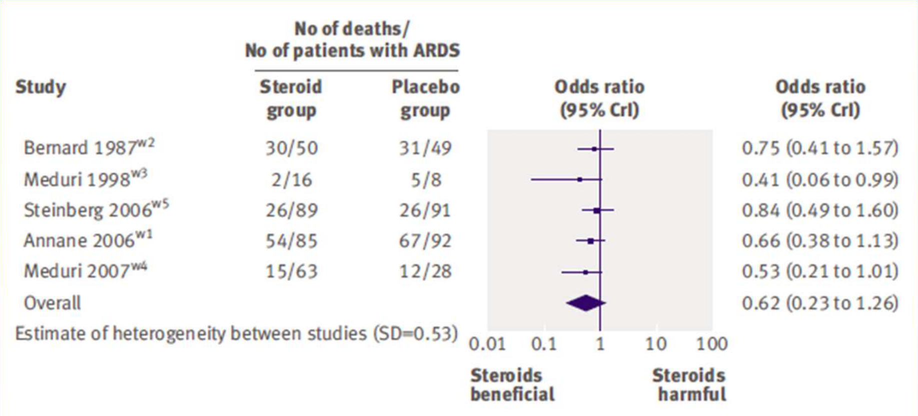
ROSE Study (n=1408)

- **Inclusion Criteria**
  - **ARDS for ≤ 48 hours**
  - **PaO2/FiO2 < 150 with PEEP ≥ 8 (or equivalent S/F)**
- **Intervention (ACURASYS Dose)**
  - **Cisatracurium bolus of 15 mg -> continuous infusion of 37.5 mg/hour for 48 hours**
  - **Higher PEEP**

ARDS Pharmacologic Rx

- Furosemide
- Cisatricurium
- Corticocosteroids

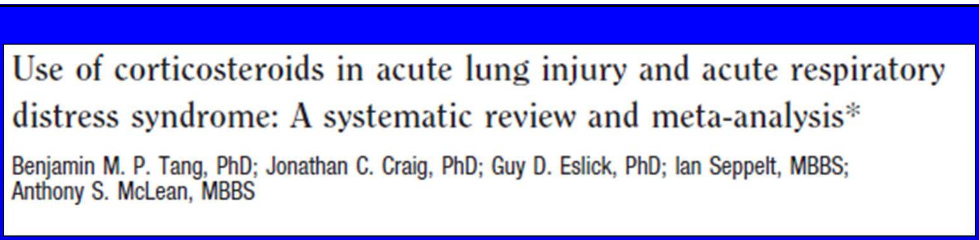
Corticosteroids for Established ARDS



Study	No of deaths/ No of patients with ARDS: Steroid group	Placebo group	Odds ratio (95% CrI)
Bernard 1987[w2]	30/50	31/49	0.75 (0.41 to 1.57)
Meduri 1998[w3]	2/16	5/8	0.41 (0.06 to 0.99)
Steinberg 2006[w5]	26/89	26/91	0.84 (0.49 to 1.60)
Annane 2006[w1]	54/85	67/92	0.66 (0.38 to 1.13)
Meduri 2007[w4]	15/63	12/28	0.53 (0.21 to 1.01)
Overall			0.62 (0.23 to 1.26)

Estimate of heterogeneity between studies (SD=0.53)

Peters BMJ 2008



Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis*

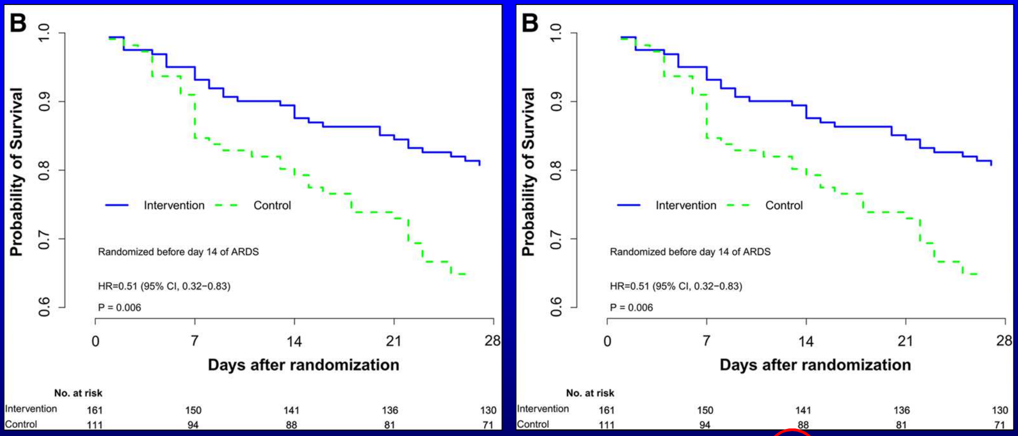
Benjamin M. P. Tang, PhD; Jonathan C. Craig, PhD; Guy D. Eslick, PhD; Ian Seppelt, MBBS; Anthony S. McLean, MBBS

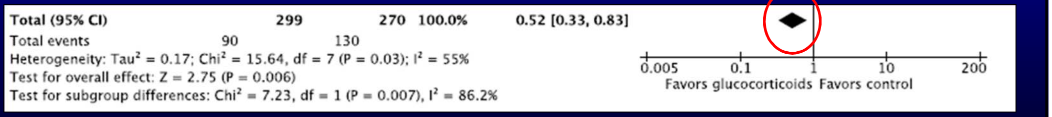
Conclusion: **The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions.**

The mortality benefits in early ARDS should be confirmed by an adequately powered randomized trial.

Crit Care Med 2009; 37:1594 –1603

Corticosteroids for Established ARDS





Total (95% CI) **299** **270** **100.0%** **0.52 [0.33, 0.83]**

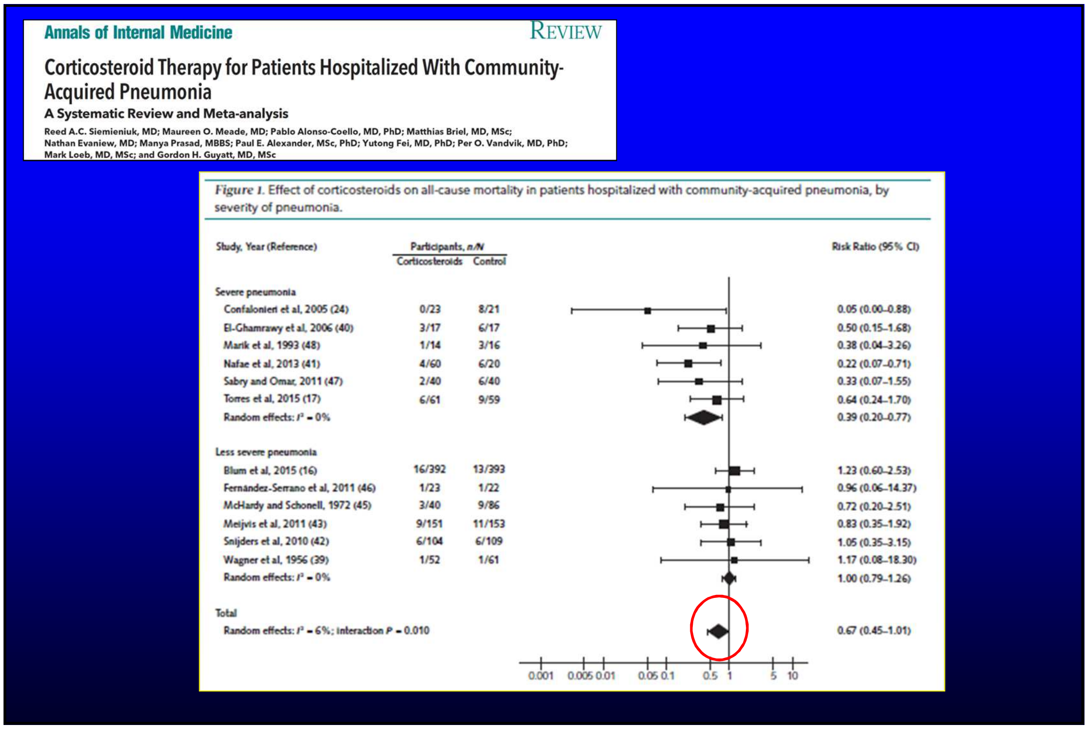
Total events 90 130

Heterogeneity: Tau^2 = 0.17; Chi^2 = 15.64, df = 7 (P = 0.03); I^2 = 55%

Test for overall effect: Z = 2.75 (P = 0.006)

Test for subgroup differences: Chi^2 = 7.23, df = 1 (P = 0.007), I^2 = 86.2%

Meduri ICM 2015



Annals of Internal Medicine REVIEW

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

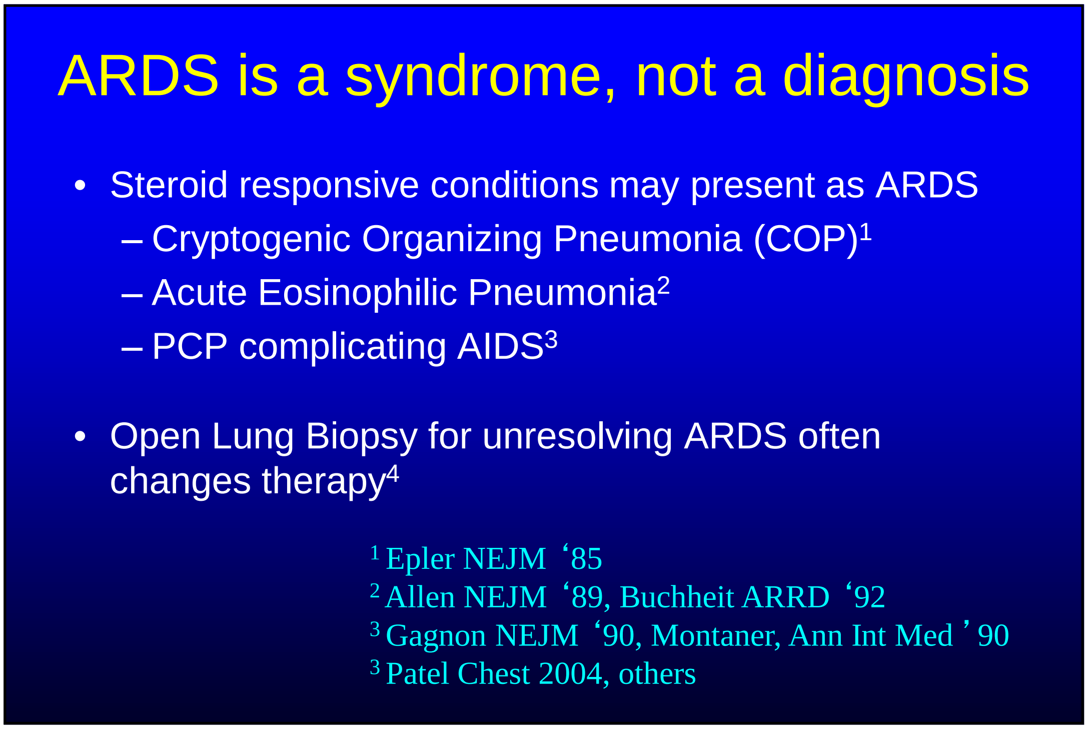
Reed A.C. Siemieniuk, MD; Maureen O. Meade, MD; Pablo Alonso-Coello, MD, PhD; Matthias Briel, MD, MSc; Nathan Evaniew, MD; Manya Prasad, MBBS; Paul E. Alexander, MSc, PhD; Yutong Fei, MD, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD, MSc; and Gordon H. Guyatt, MD, MSc

Figure 1. Effect of corticosteroids on all-cause mortality in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.

Study, Year (Reference)	Participants, *n/N*		Risk Ratio (95% CI)
	Corticosteroids	Control	
Severe pneumonia			
Confalonieri et al, 2005 (24)	0/23	8/21	0.05 (0.00–0.88)
El-Ghamrawy et al, 2006 (40)	3/17	6/17	0.50 (0.15–1.68)
Marik et al, 1993 (48)	1/14	3/16	0.38 (0.04–3.26)
Nafae et al, 2013 (41)	4/60	6/20	0.22 (0.07–0.71)
Sabry and Omar, 2011 (47)	2/40	6/40	0.33 (0.07–1.55)
Torres et al, 2015 (17)	6/61	9/59	0.64 (0.24–1.70)
Random effects: $I^2 = 0\%$			0.39 (0.20–0.77)
Less severe pneumonia			
Blum et al, 2015 (16)	16/392	13/393	1.23 (0.60–2.53)
Fernández-Serrano et al, 2011 (46)	1/23	1/22	0.96 (0.06–14.37)
McHardy and Schonell, 1972 (45)	3/40	9/86	0.72 (0.20–2.51)
Meijvis et al, 2011 (43)	9/151	11/153	0.83 (0.35–1.92)
Snijders et al, 2010 (42)	6/104	6/109	1.05 (0.35–3.15)
Wagner et al, 1956 (39)	1/52	1/61	1.17 (0.08–18.30)
Random effects: $I^2 = 0\%$			1.00 (0.79–1.26)
Total			
Random effects: $I^2 = 6\%$; interaction $P = 0.010$			0.67 (0.45–1.01)

Words of caution…

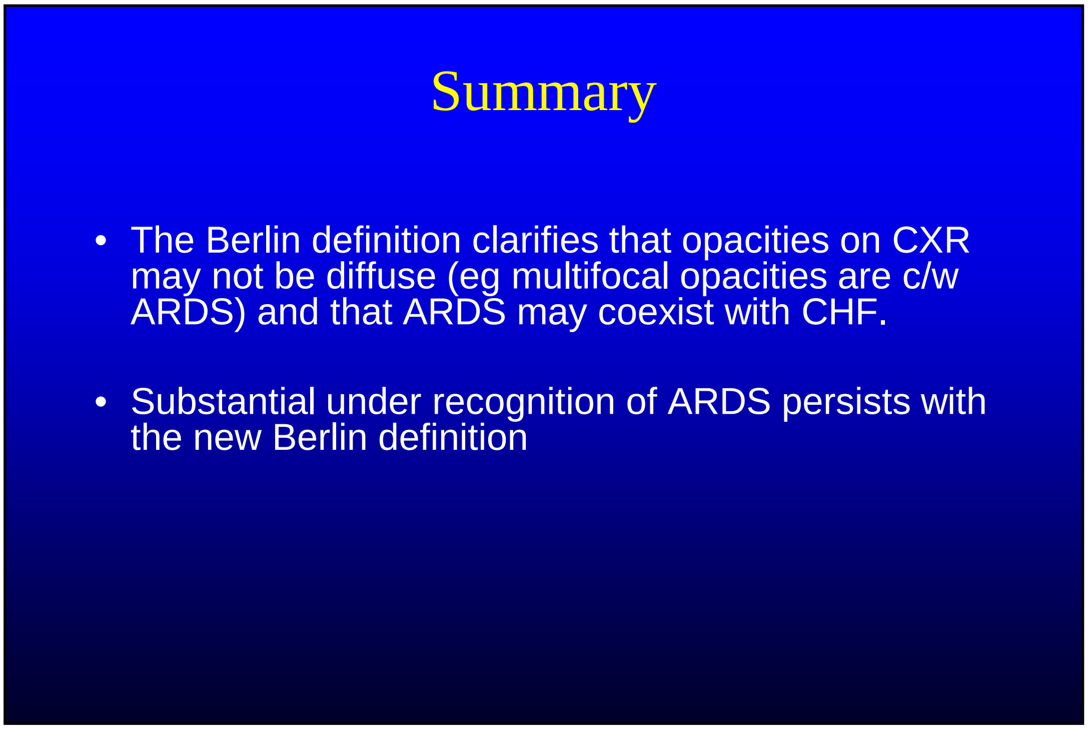
- Neuromuscular weakness following ARDS persists for years, interferes with ADLs and return to work
  - Herridge NEJM 2003, 2006
- Steroid Rx a/w doubling of mortality for severe H1N1
  - Matthay, AJRCCM 2011



ARDS is a syndrome, not a diagnosis

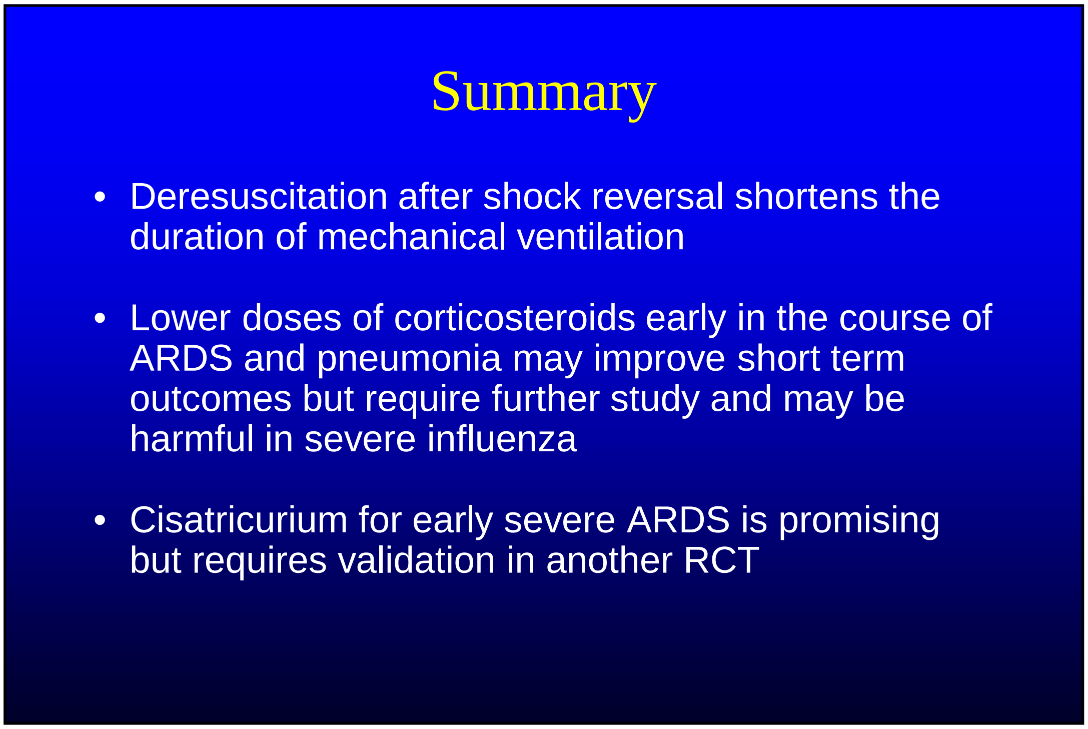
- Steroid responsive conditions may present as ARDS
  - Cryptogenic Organizing Pneumonia (COP)[1]
  - Acute Eosinophilic Pneumonia[2]
  - PCP complicating AIDS[3]
- Open Lung Biopsy for unresolving ARDS often changes therapy[4]

[1] Epler NEJM ‘85
[2] Allen NEJM ‘89, Buchheit ARRD ‘92
[3] Gagnon NEJM ‘90, Montaner, Ann Int Med ’90
[3] Patel Chest 2004, others



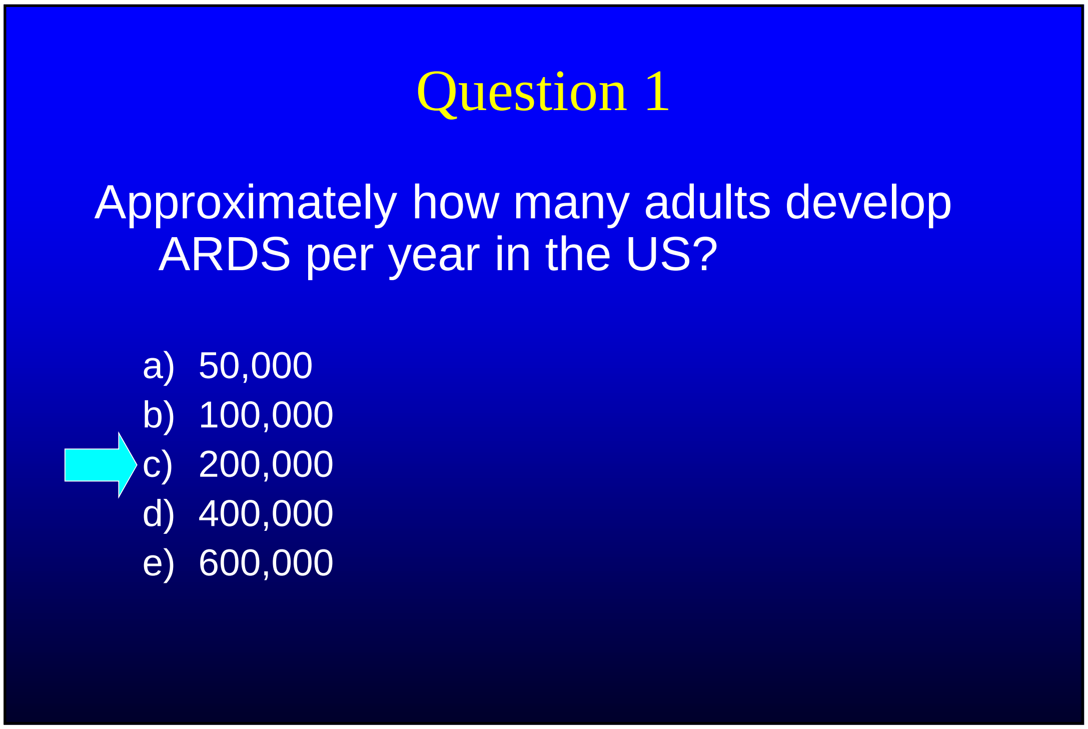
Summary

- The Berlin definition clarifies that opacities on CXR may not be diffuse (eg multifocal opacities are c/w ARDS) and that ARDS may coexist with CHF.
- Substantial under recognition of ARDS persists with the new Berlin definition



Summary

- Deresuscitation after shock reversal shortens the duration of mechanical ventilation
- Lower doses of corticosteroids early in the course of ARDS and pneumonia may improve short term outcomes but require further study and may be harmful in severe influenza
- Cisatricurium for early severe ARDS is promising but requires validation in another RCT



Question 1

Approximately how many adults develop ARDS per year in the US?

a) 50,000
b) 100,000
[✓ c) 200,000]
d) 400,000
e) 600,000

Question 2

A 45 year old with bacteremic pneumococcal pneumonia, shock and ARDS is recovering by ICU day two. You wish to use a conservative fluid management strategy. The following are part of the ARDS Network FACTT approach EXCEPT:

a) No furosemide within 12 hours of vasopressor use

False b) Maintenance fluids were allowed during shock

c) If a fluid bolus was given for hypotension, furosemide should be held for 12 hours

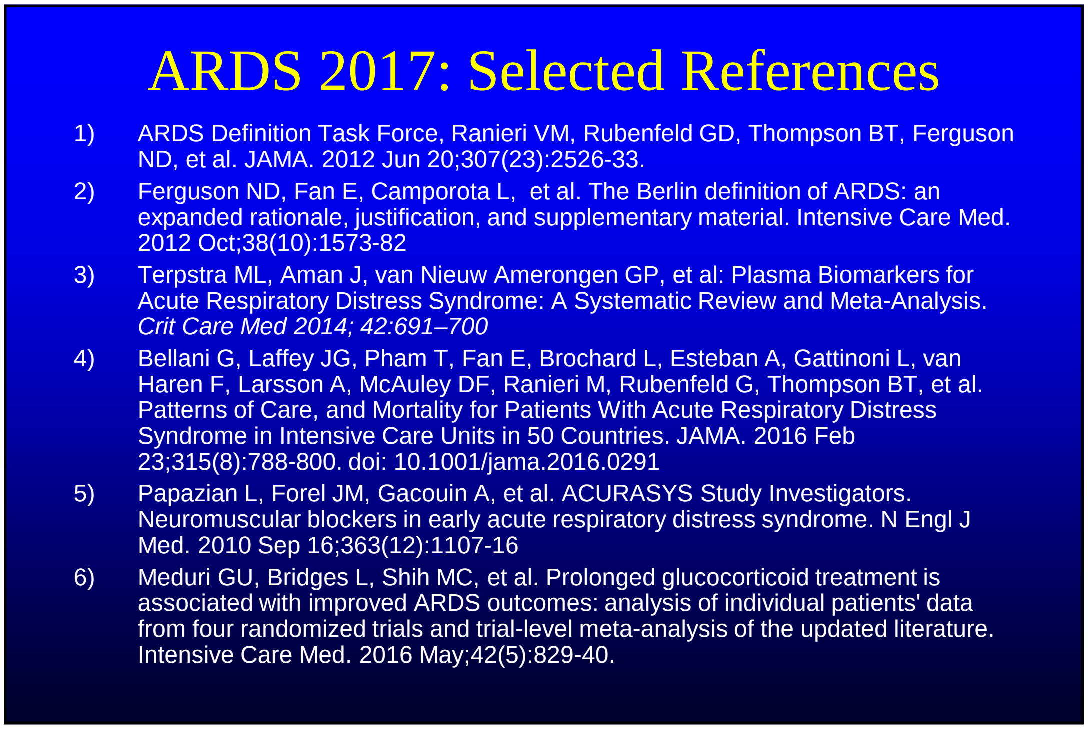
d) Furosemide was held if creatinine was increasing and the urine sediment suggested tubular injury

e) Furosemide by continuous infusion was an acceptable alternative to intermittent bolus dosing

Question 3

False
Apparent Benefit in P/F < 120

- The ACURASYS trial suggests cisatricurium may be beneficial during the first two days of severe ARDS (True/False)
  - All patients meeting the Berlin definition of ARDS were shown to benefit
  - A 15 mg bolus was followed by 37.5 mg/hour was used
  - Another trial is needed before cisatracurium at this dose can be recommended for routine management of ARDS



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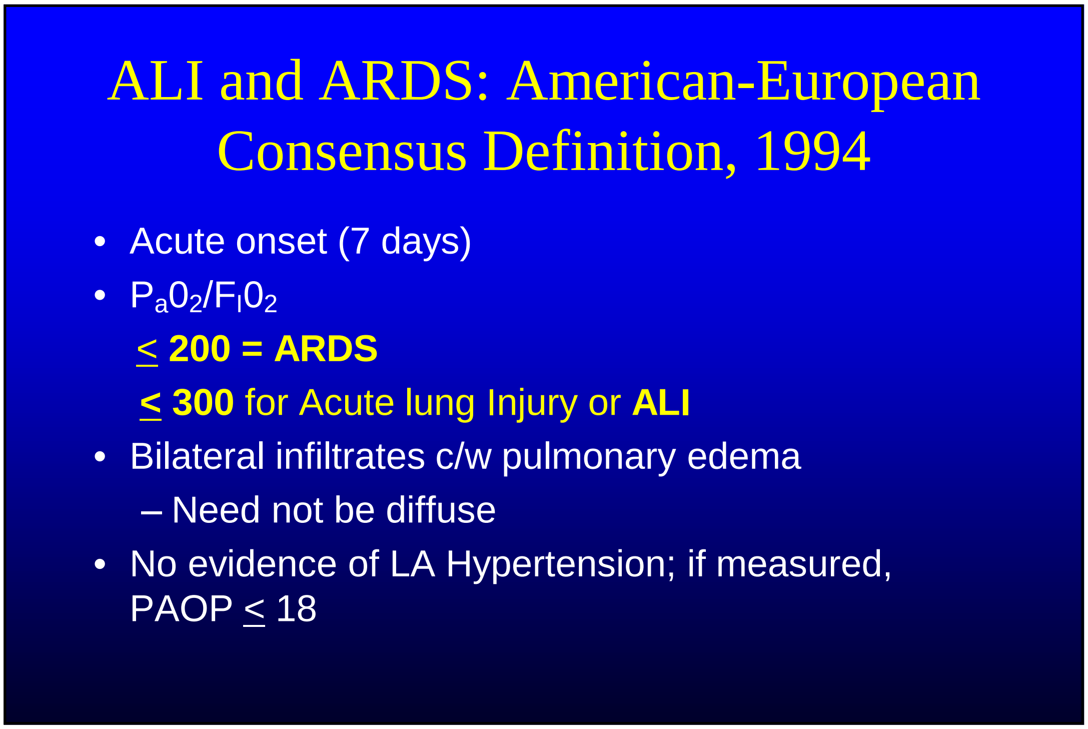
1) ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, et al. JAMA. 2012 Jun 20;307(23):2526-33.
2) Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012 Oct;38(10):1573-82
3) Terpstra ML, Aman J, van Nieuw Amerongen GP, et al: Plasma Biomarkers for Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis. *Crit Care Med 2014; 42:691–700*
4) Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, et al. Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016 Feb 23;315(8):788-800. doi: 10.1001/jama.2016.0291
5) Papazian L, Forel JM, Gacouin A, et al. ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010 Sep 16;363(12):1107-16
6) Meduri GU, Bridges L, Shih MC, et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med. 2016 May;42(5):829-40.

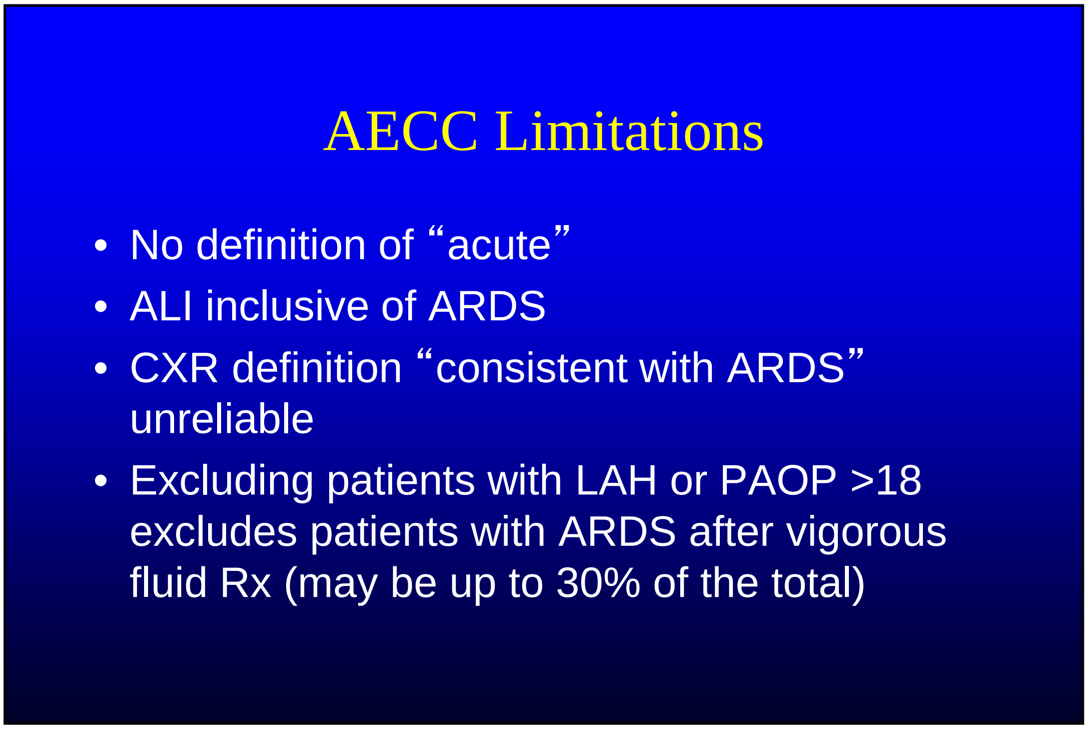


ALI and ARDS: American-European Consensus Definition, 1994

- Acute onset (7 days)
- P_a0_2/F_I0_2

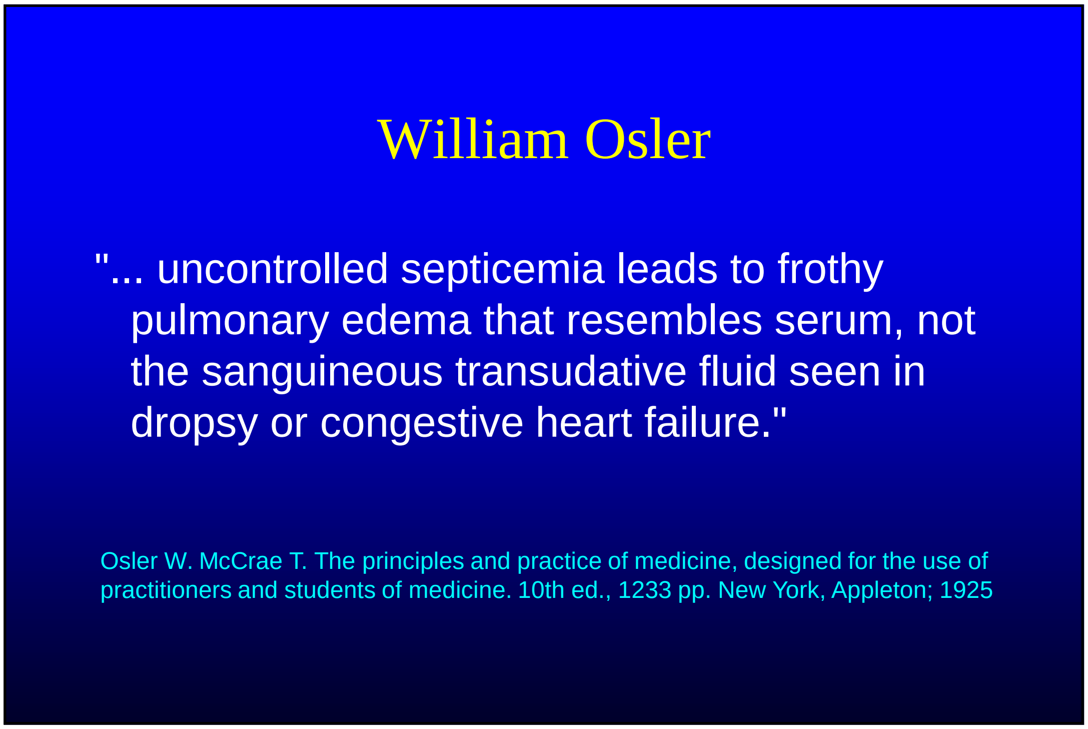
  ≤ 200 = ARDS

  ≤ 300 for Acute lung Injury or **ALI**
- Bilateral infiltrates c/w pulmonary edema
  - Need not be diffuse
- No evidence of LA Hypertension; if measured, PAOP ≤ 18



AECC Limitations

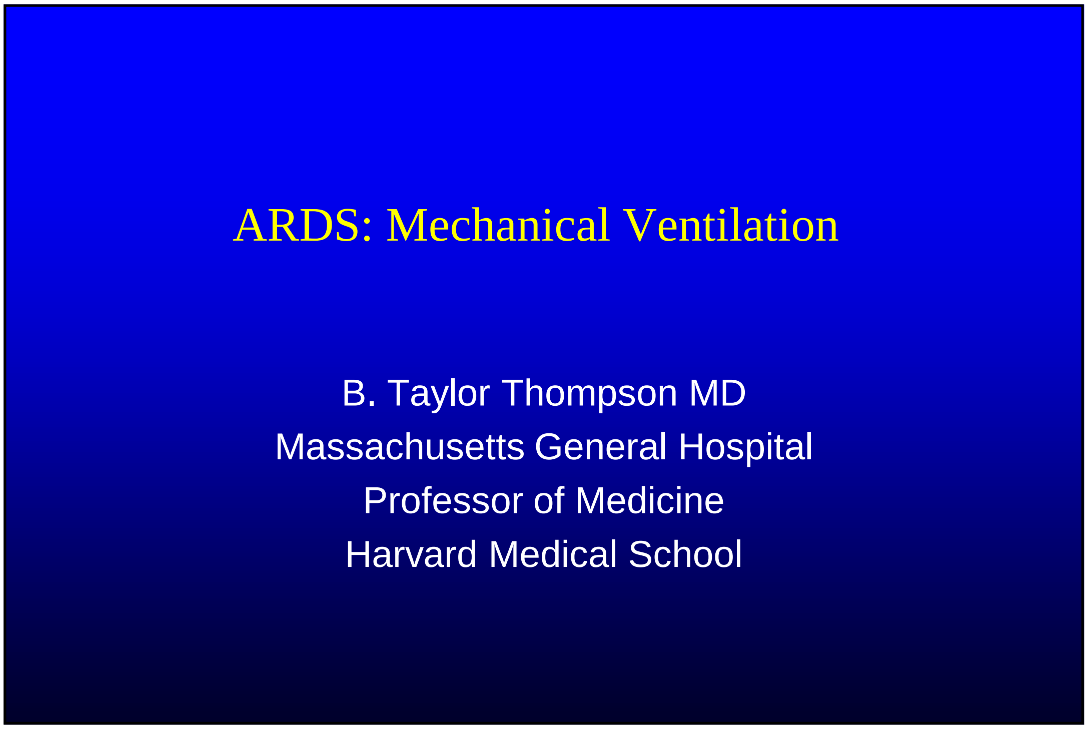
- No definition of “acute”
- ALI inclusive of ARDS
- CXR definition “consistent with ARDS” unreliable
- Excluding patients with LAH or PAOP >18 excludes patients with ARDS after vigorous fluid Rx (may be up to 30% of the total)



William Osler

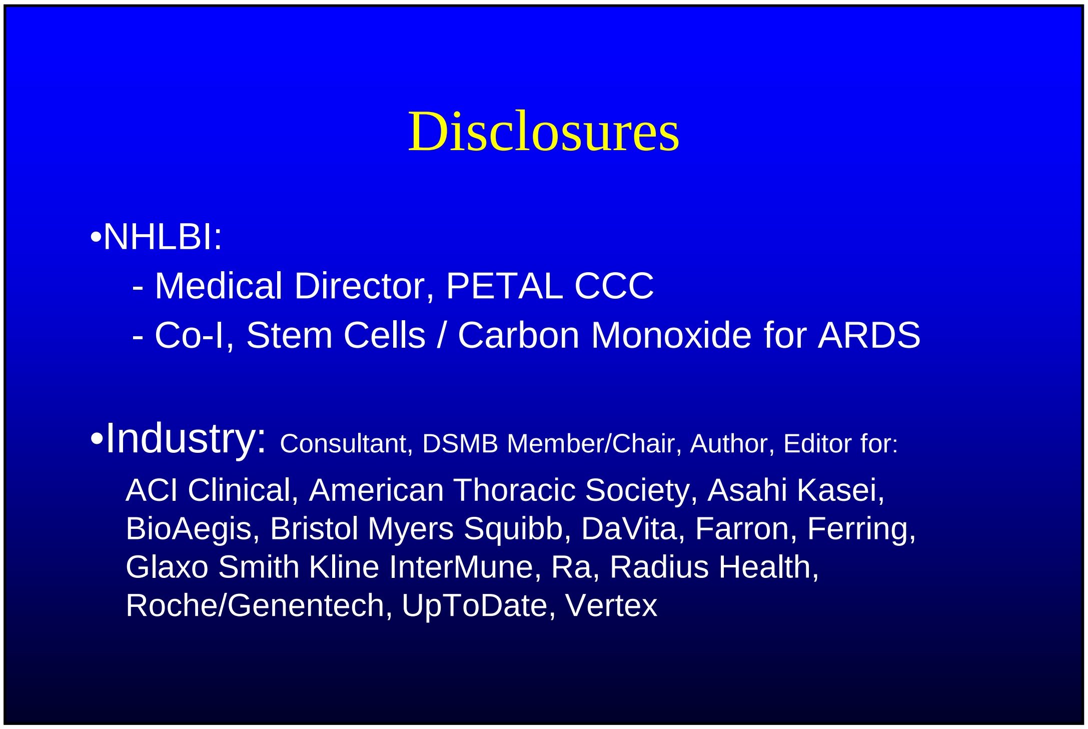
"... uncontrolled septicemia leads to frothy pulmonary edema that resembles serum, not the sanguineous transudative fluid seen in dropsy or congestive heart failure."

Osler W. McCrae T. The principles and practice of medicine, designed for the use of practitioners and students of medicine. 10th ed., 1233 pp. New York, Appleton; 1925



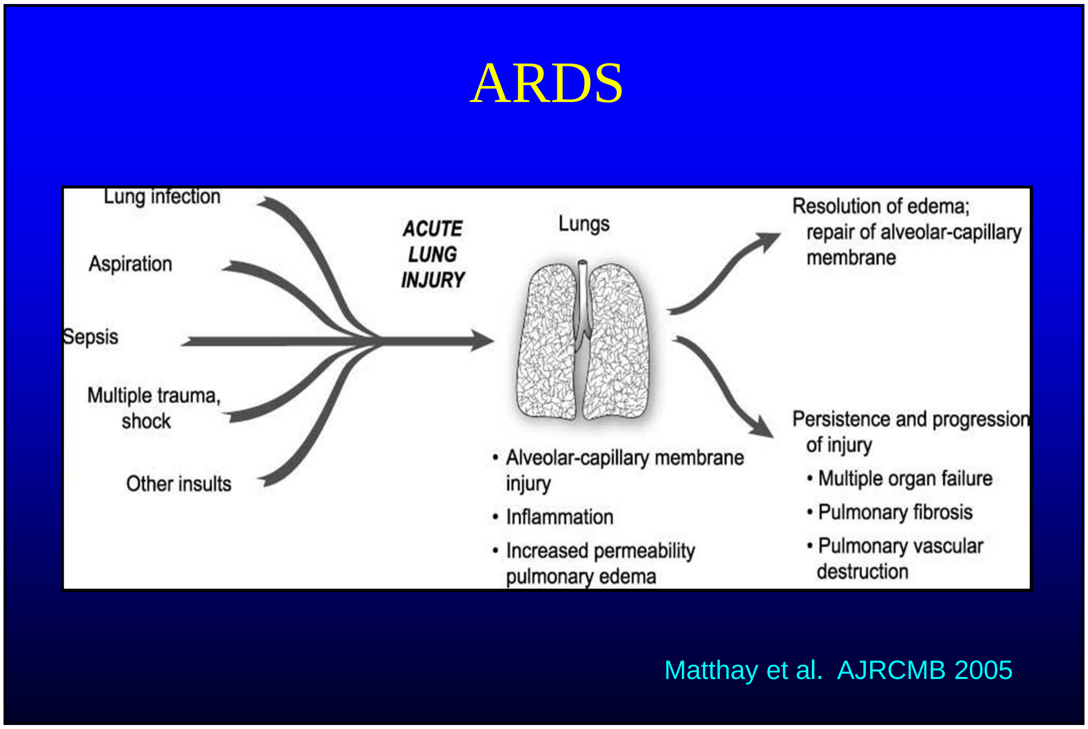
ARDS: Mechanical Ventilation

B. Taylor Thompson MD
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School



Disclosures

- NHLBI:
  - Medical Director, PETAL CCC
  - Co-I, Stem Cells / Carbon Monoxide for ARDS
- Industry: Consultant, DSMB Member/Chair, Author, Editor for: ACI Clinical, American Thoracic Society, Asahi Kasei, BioAegis, Bristol Myers Squibb, DaVita, Farron, Ferring, Glaxo Smith Kline InterMune, Ra, Radius Health, Roche/Genentech, UpToDate, Vertex



ARDS

Lung infection

Aspiration

Sepsis

Multiple trauma, shock

Other insults

ACUTE LUNG INJURY

Lungs

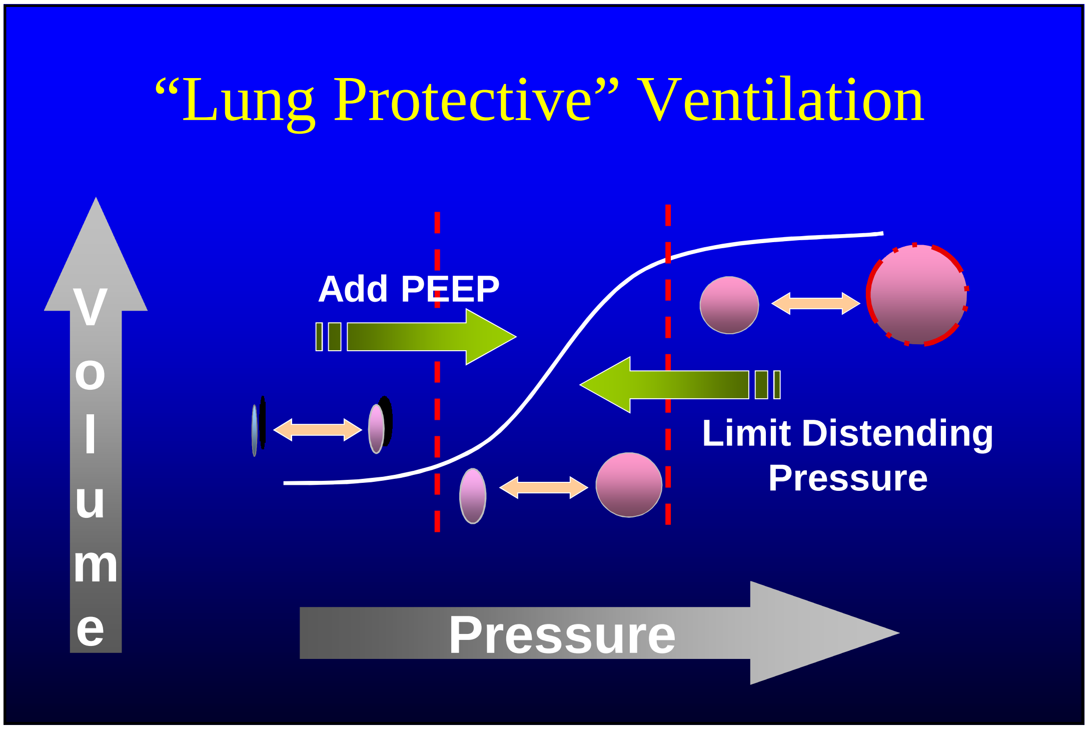
- Alveolar-capillary membrane injury
- Inflammation
- Increased permeability pulmonary edema

Resolution of edema; repair of alveolar-capillary membrane

Persistence and progression of injury

- Multiple organ failure
- Pulmonary fibrosis
- Pulmonary vascular destruction

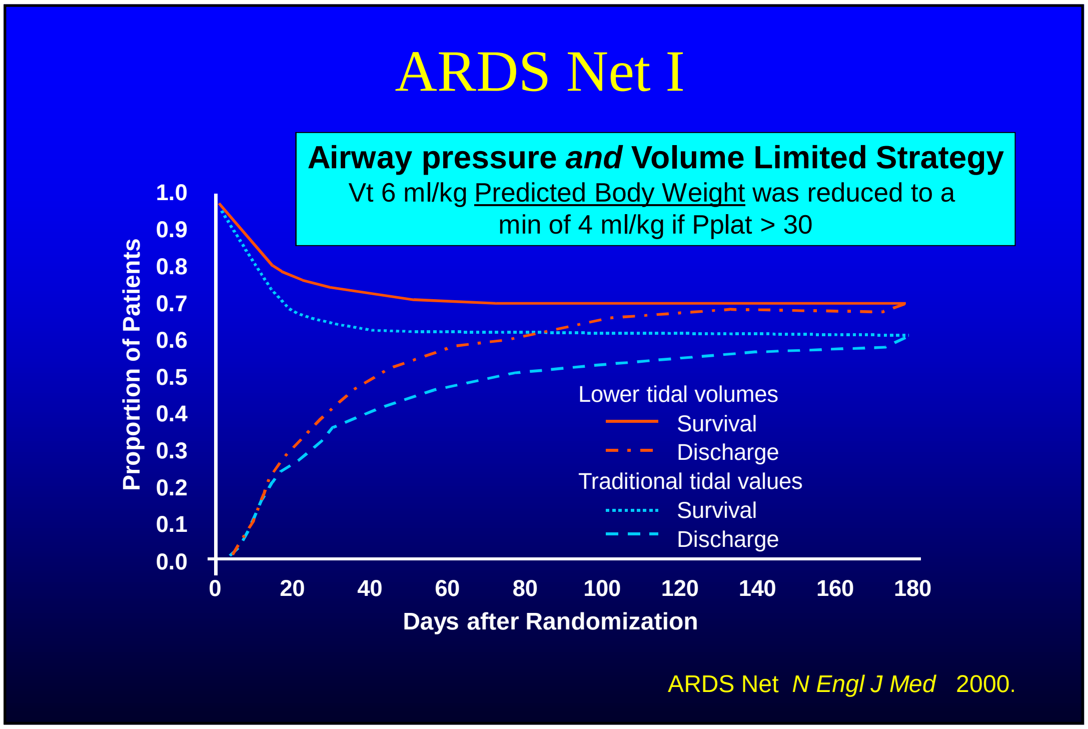
Matthay et al. AJRCMB 2005



"Lung Protective" Ventilation

Add PEEP

Limit Distending Pressure

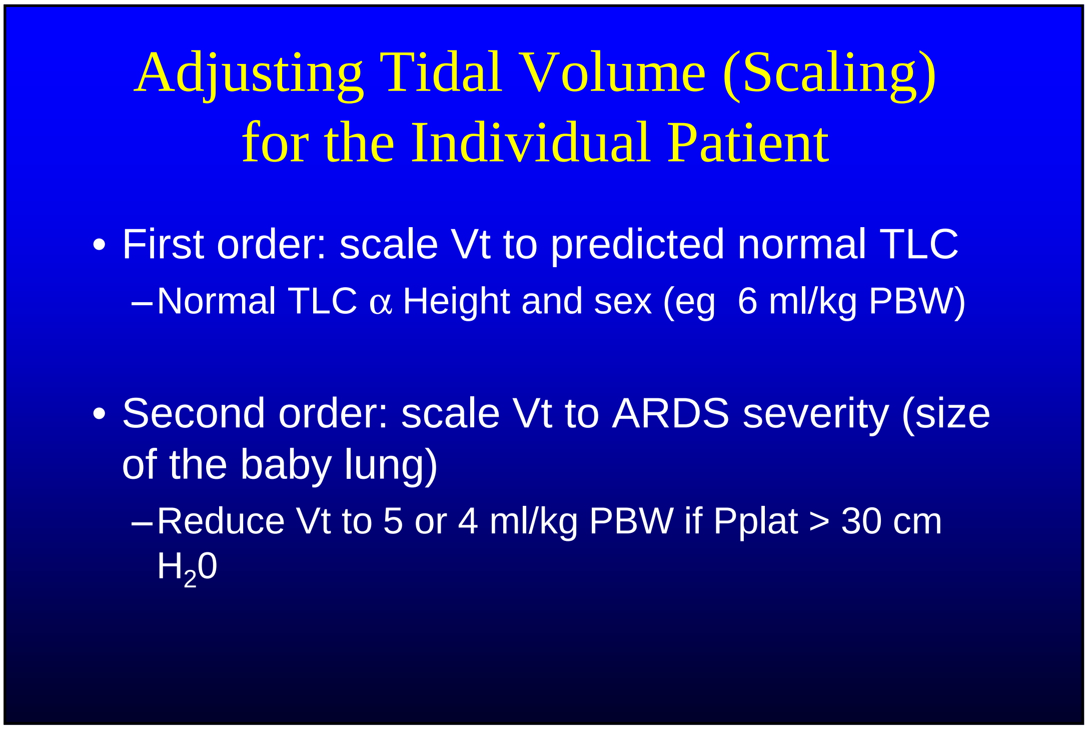


ARDS Net I

Airway pressure *and* Volume Limited Strategy

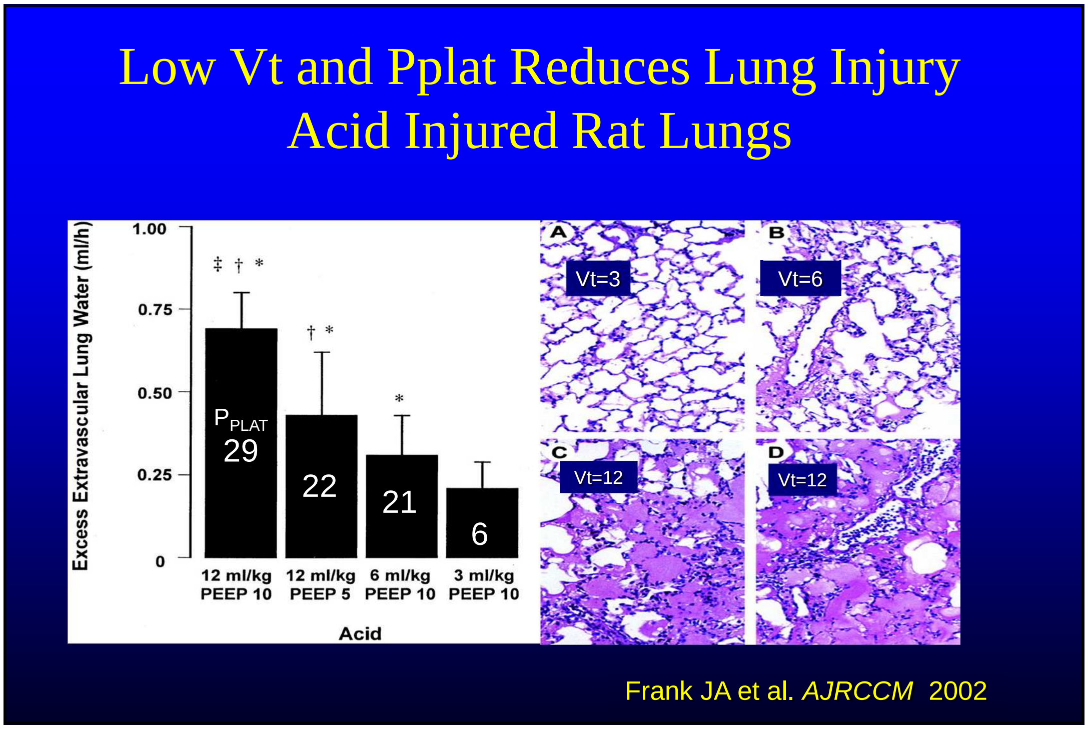
Vt 6 ml/kg Predicted Body Weight was reduced to a min of 4 ml/kg if Pplat > 30

ARDS Net *N Engl J Med* 2000.



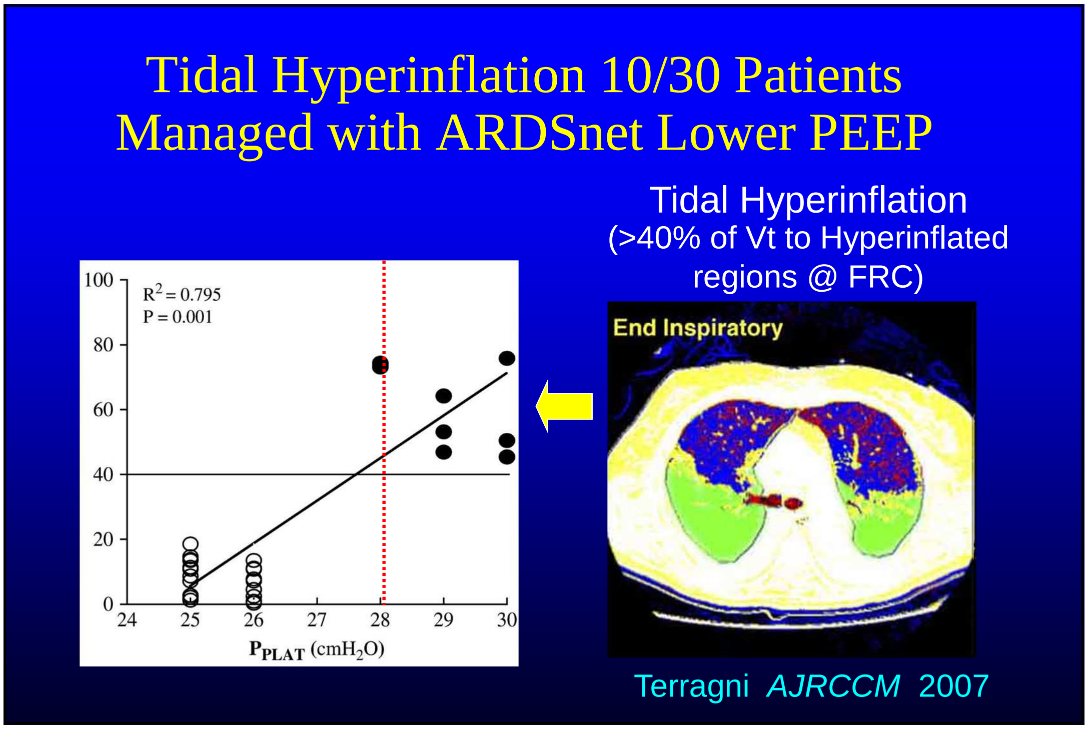
Adjusting Tidal Volume (Scaling) for the Individual Patient

- First order: scale Vt to predicted normal TLC
  - Normal TLC α Height and sex (eg 6 ml/kg PBW)
- Second order: scale Vt to ARDS severity (size of the baby lung)
  - Reduce Vt to 5 or 4 ml/kg PBW if Pplat > 30 cm H_20



Low Vt and Pplat Reduces Lung Injury Acid Injured Rat Lungs

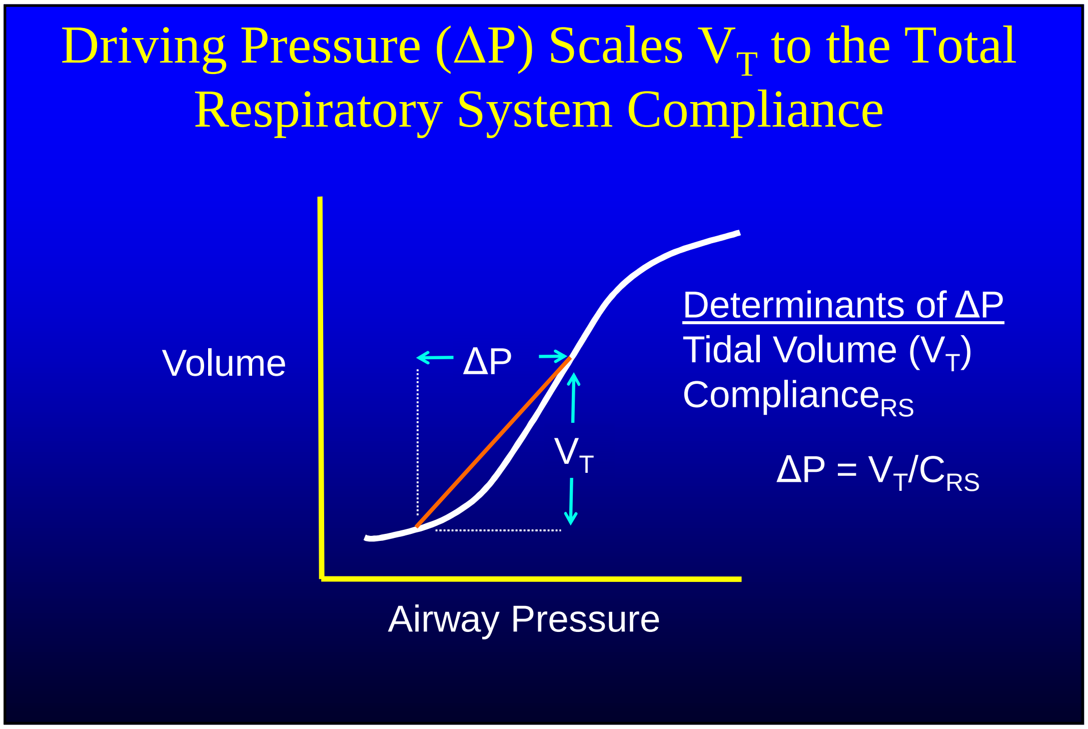
Frank JA et al. *AJRCCM* 2002



Tidal Hyperinflation 10/30 Patients Managed with ARDSnet Lower PEEP

Tidal Hyperinflation
(>40% of Vt to Hyperinflated regions @ FRC)

Terragni *AJRCCM* 2007

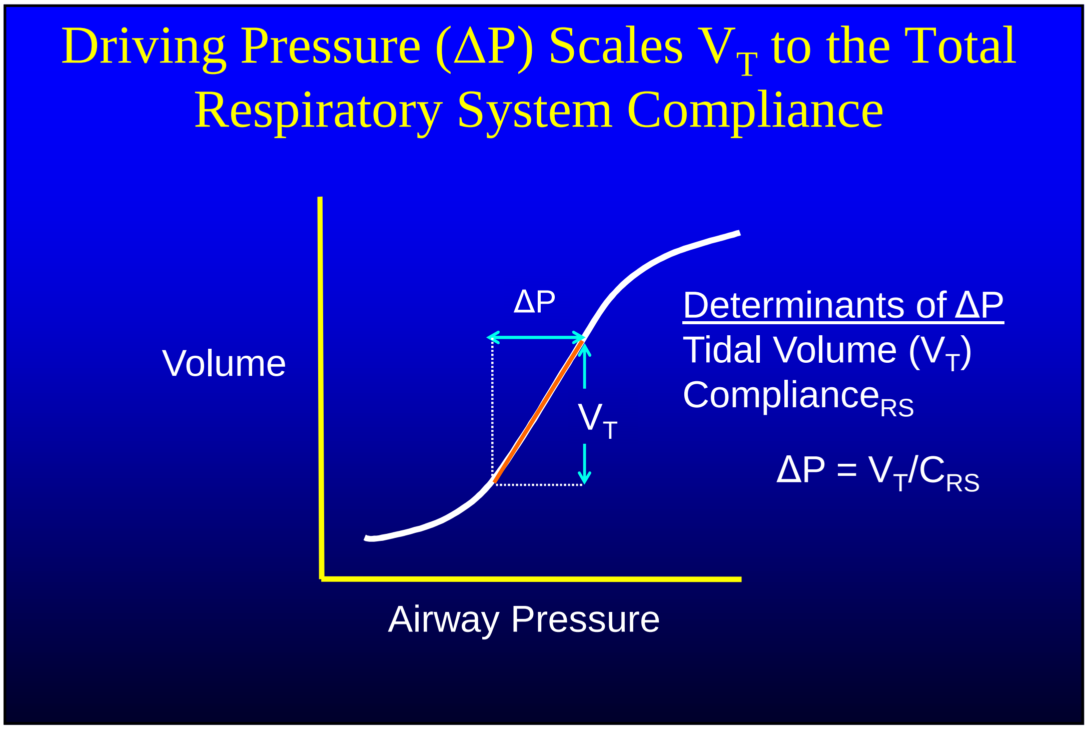


Driving Pressure (ΔP) Scales V_T to the Total Respiratory System Compliance

Volume
ΔP
V_T
Airway Pressure

Determinants of ΔP
Tidal Volume (V_T)
$Compliance_{RS}$

$\Delta P = V_T/C_{RS}$



Driving Pressure (ΔP) Scales V_T to the Total Respiratory System Compliance

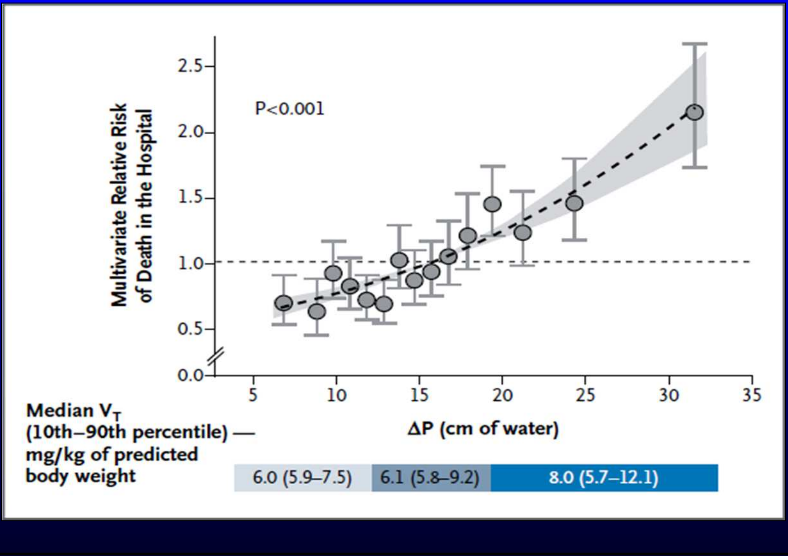
Volume
ΔP
V_T
Airway Pressure

Determinants of ΔP
Tidal Volume (V_T)
$Compliance_{RS}$

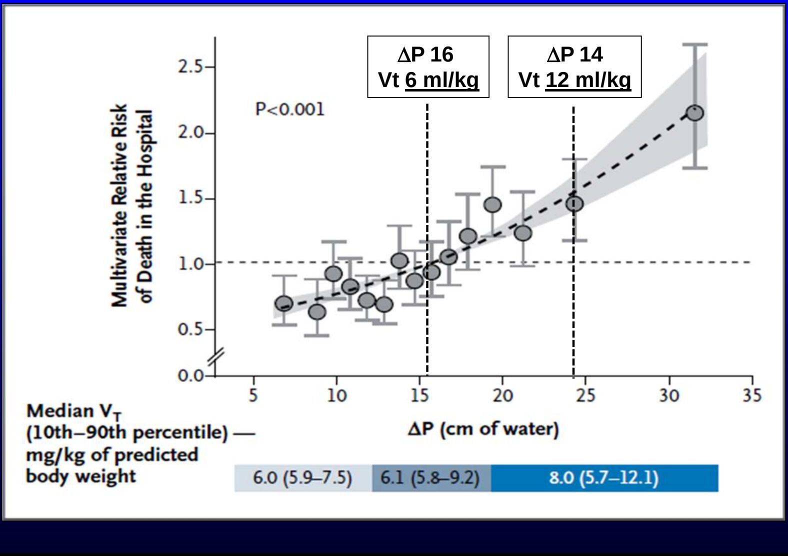
$\Delta P = V_T/C_{RS}$

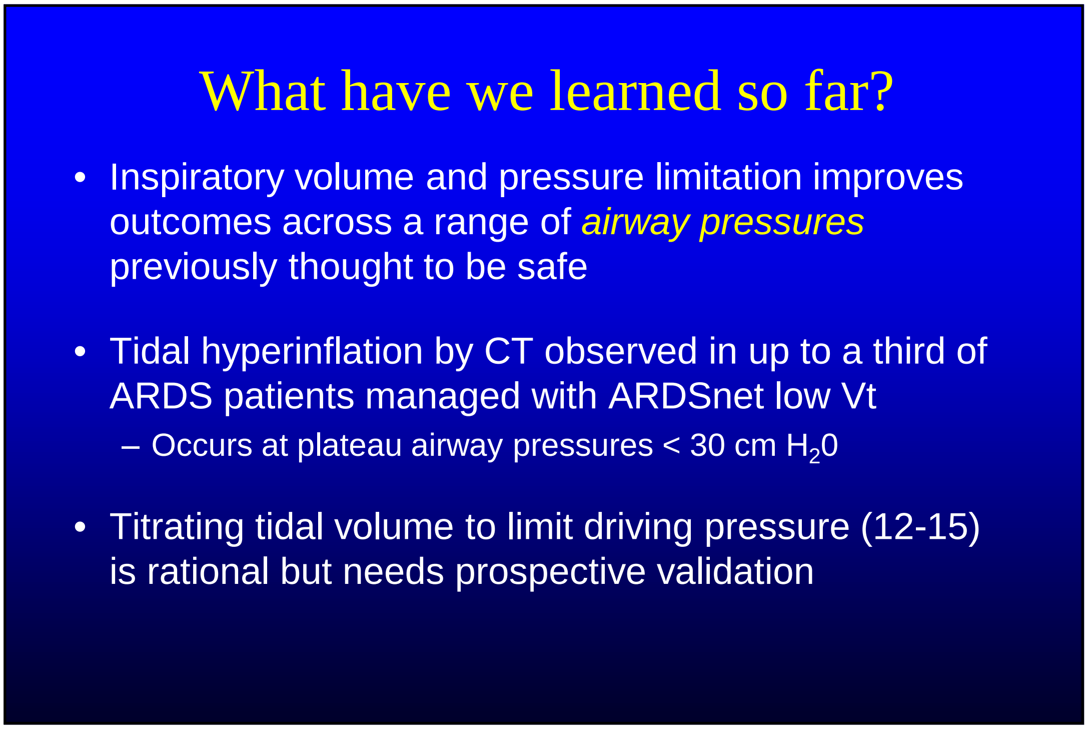
Patient Level Mediation Analysis (n=3,562)

Amato *N Engl J Med* 2015



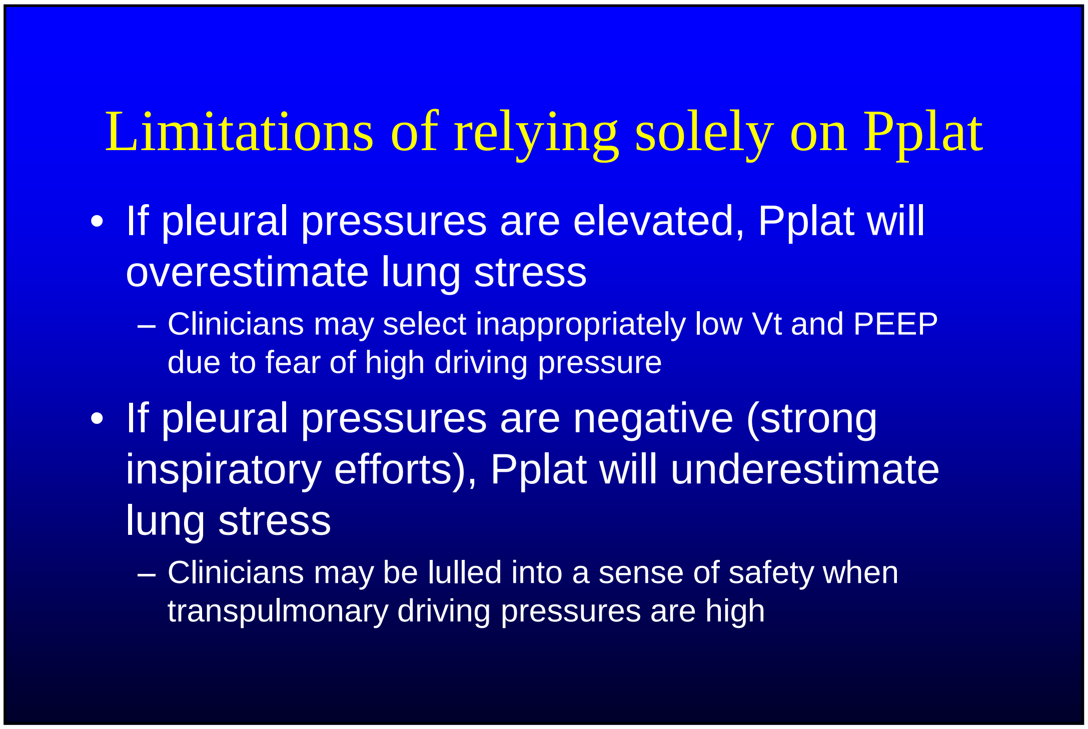
ARDS Network Mean Driving Pressures in the 6 and 12 ml/kg PBW Vt Groups





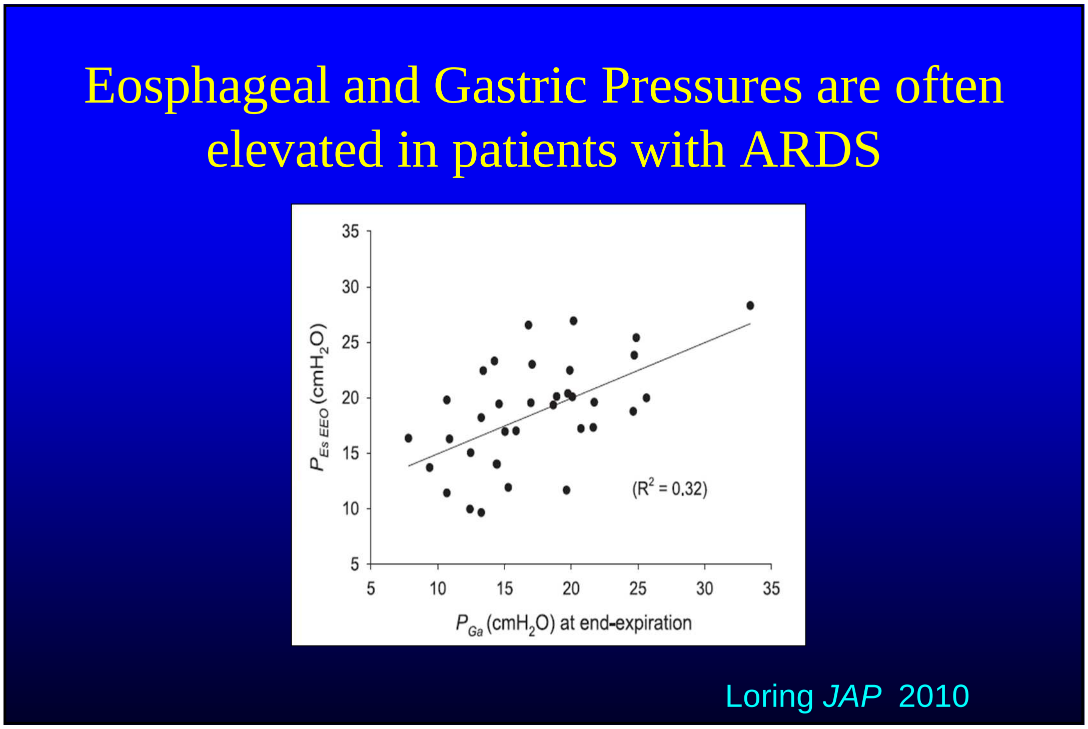
What have we learned so far?

- Inspiratory volume and pressure limitation improves outcomes across a range of *airway pressures* previously thought to be safe
- Tidal hyperinflation by CT observed in up to a third of ARDS patients managed with ARDSnet low Vt
  - Occurs at plateau airway pressures < 30 cm H_20
- Titrating tidal volume to limit driving pressure (12-15) is rational but needs prospective validation



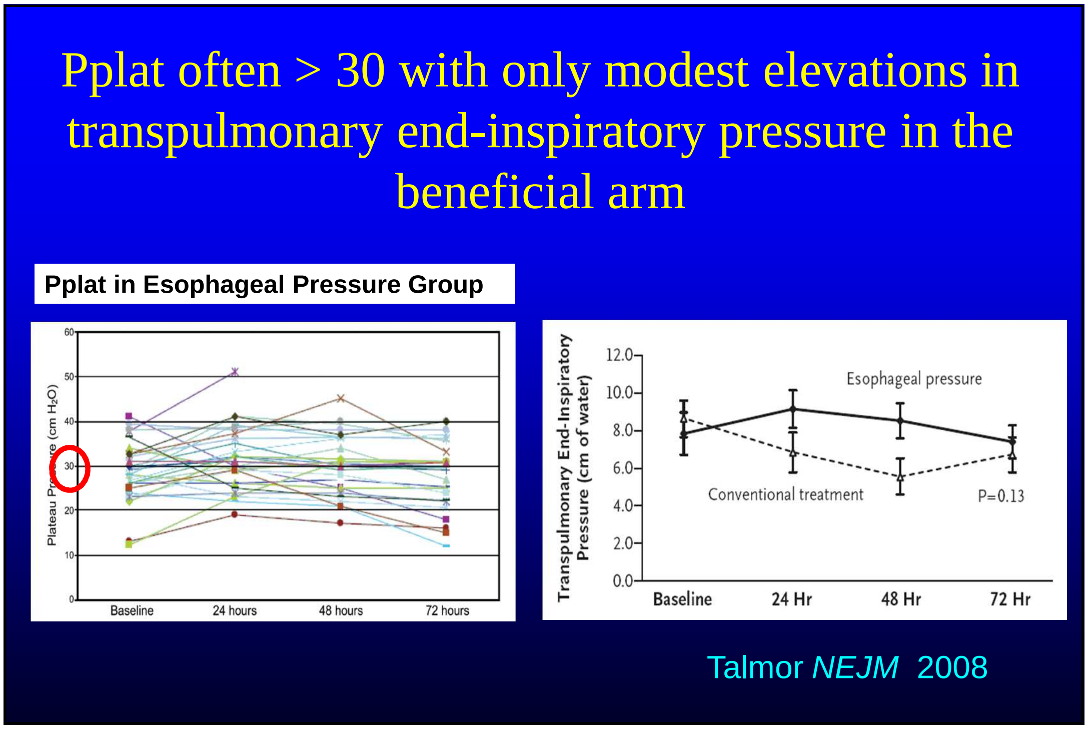
Limitations of relying solely on Pplat

- If pleural pressures are elevated, Pplat will overestimate lung stress
  - Clinicians may select inappropriately low Vt and PEEP due to fear of high driving pressure
- If pleural pressures are negative (strong inspiratory efforts), Pplat will underestimate lung stress
  - Clinicians may be lulled into a sense of safety when transpulmonary driving pressures are high



Eosphageal and Gastric Pressures are often elevated in patients with ARDS

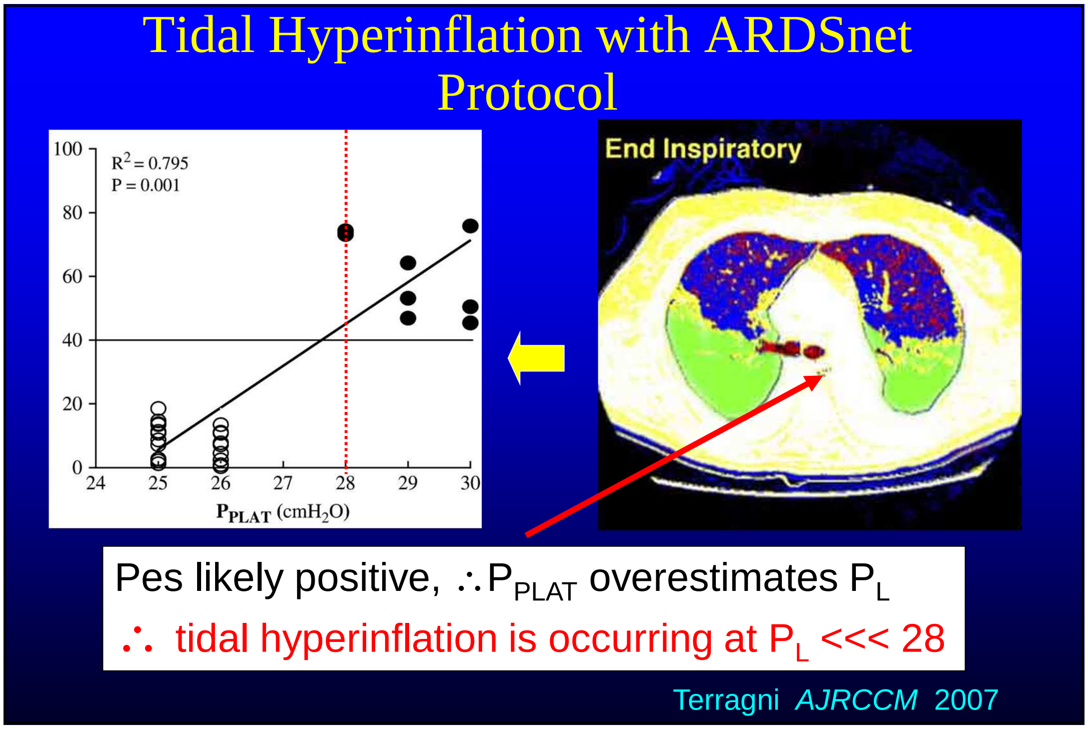
Loring *JAP* 2010



Pplat often > 30 with only modest elevations in transpulmonary end-inspiratory pressure in the beneficial arm

Pplat in Esophageal Pressure Group

Talmor *NEJM* 2008

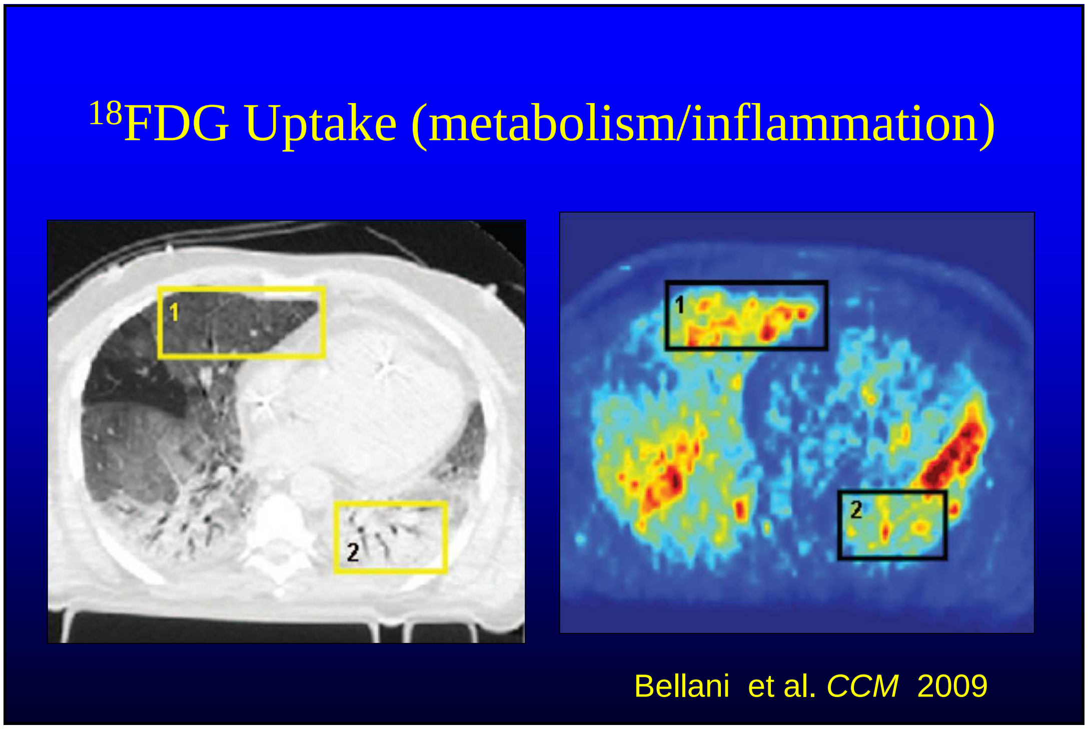


Tidal Hyperinflation with ARDSnet Protocol

Pes likely positive, ∴P_{PLAT} overestimates P_L

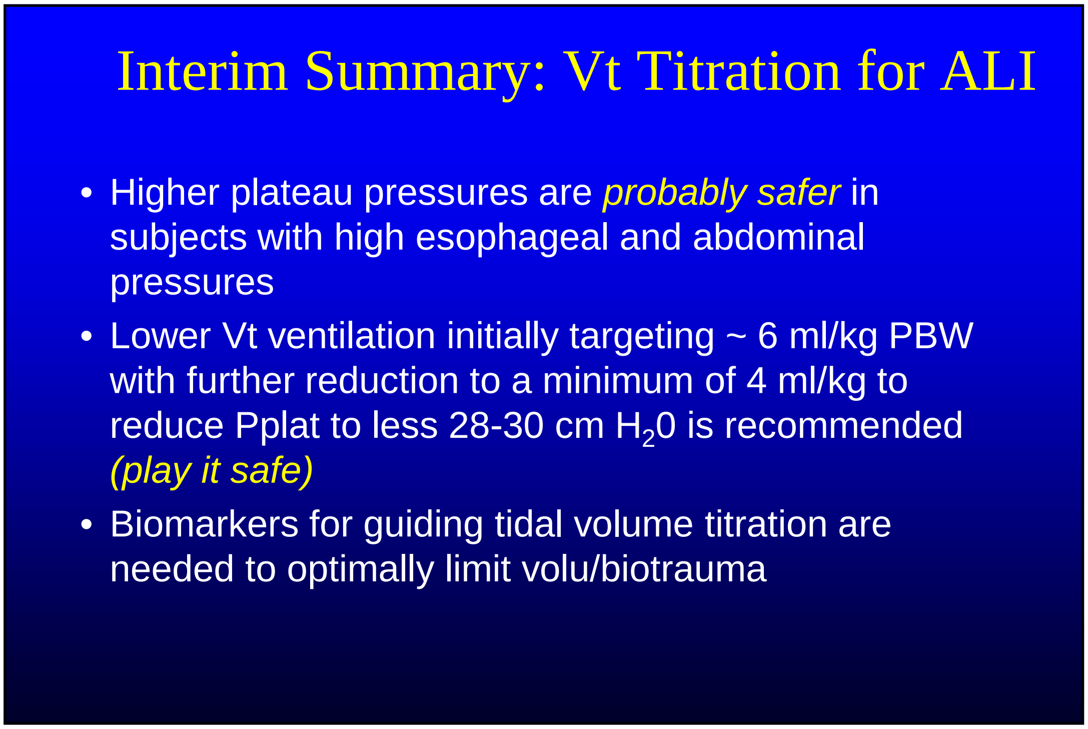
∴ tidal hyperinflation is occurring at P_L <<< 28

Terragni *AJRCCM* 2007



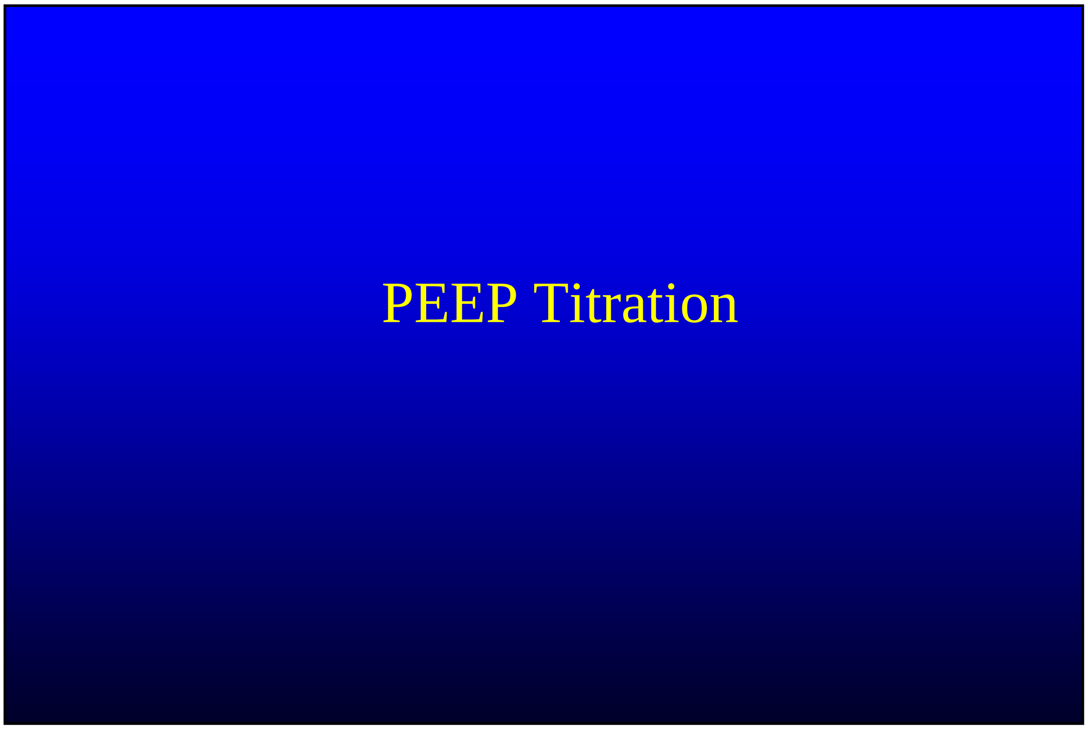
^{18}FDG Uptake (metabolism/inflammation)

Bellani et al. *CCM* 2009

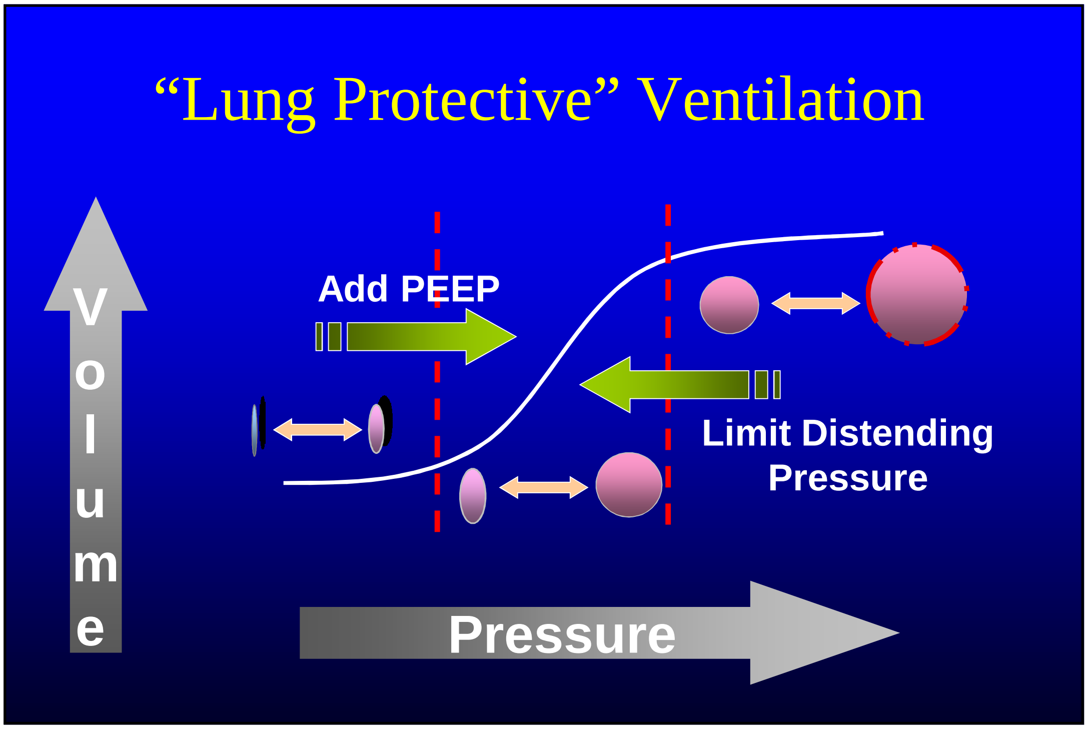


Interim Summary: Vt Titration for ALI

- Higher plateau pressures are *probably safer* in subjects with high esophageal and abdominal pressures
- Lower Vt ventilation initially targeting ~ 6 ml/kg PBW with further reduction to a minimum of 4 ml/kg to reduce Pplat to less 28-30 cm H_20 is recommended *(play it safe)*
- Biomarkers for guiding tidal volume titration are needed to optimally limit volu/biotrauma



PEEP Titration



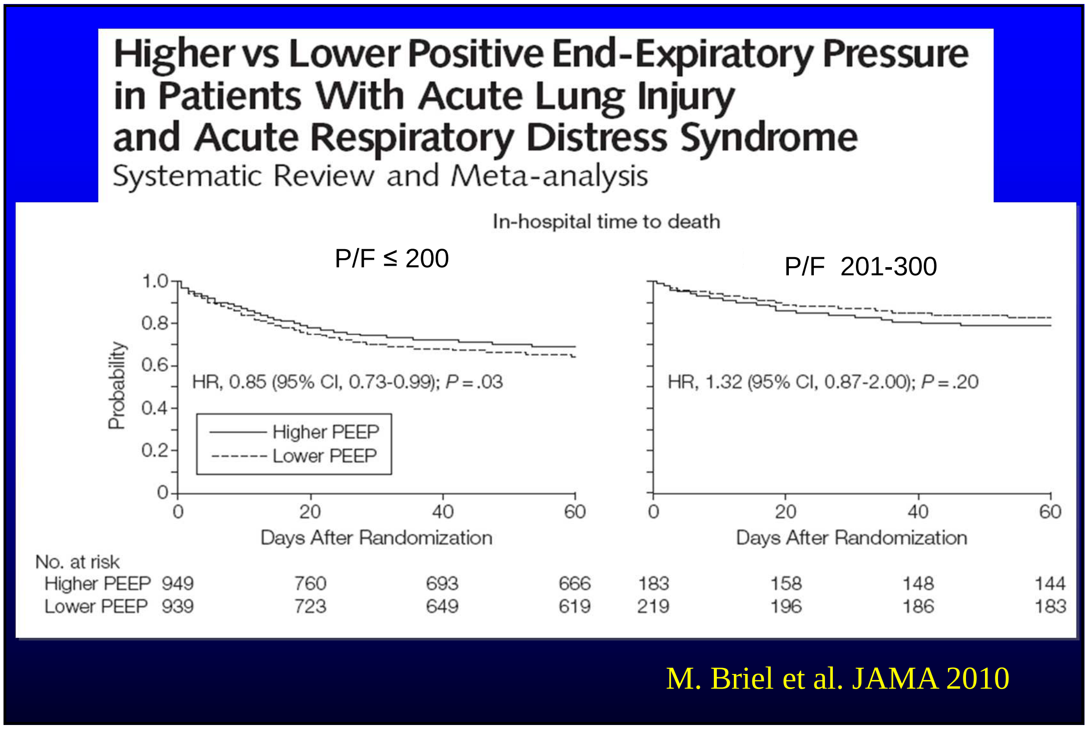
“Lung Protective” Ventilation

Add PEEP

Limit Distending Pressure

Volume

Pressure



Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome

Systematic Review and Meta-analysis

In-hospital time to death

HR, 0.85 (95% CI, 0.73-0.99); *P* = .03

HR, 1.32 (95% CI, 0.87-2.00); *P* = .20

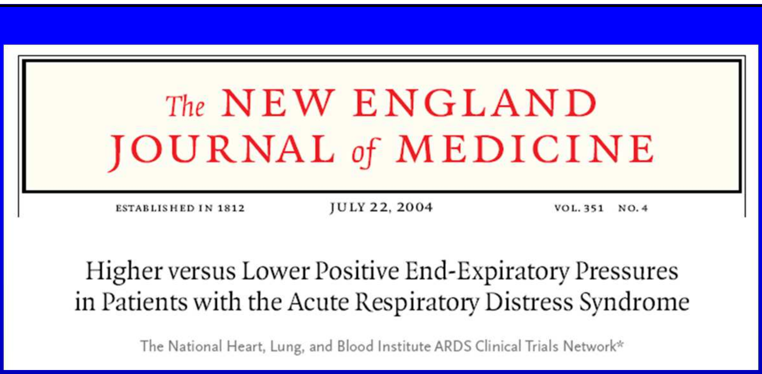
No. at risk	0	20	40	60	0	20	40	60
Higher PEEP	949	760	693	666	183	158	148	144
Lower PEEP	939	723	649	619	219	196	186	183

M. Briel et al. JAMA 2010

PEEP Titration Methods

- PEEP F_I02 scales
- Tidal Compliance or “Driving Pressure”
- Stress Index
- Esophageal Pressure
- Imaging (CT, impedance)

Chuimello CCM 2014

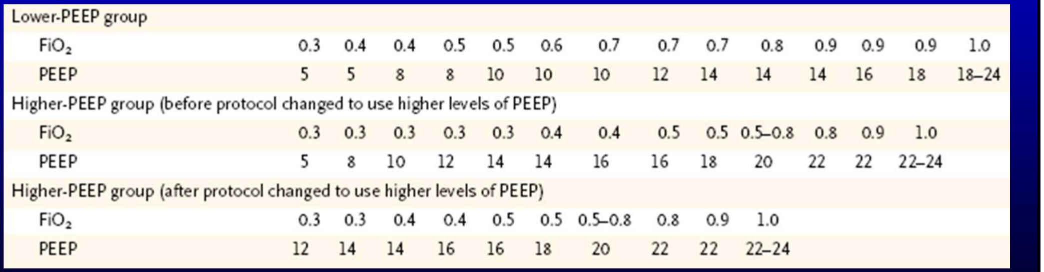


The NEW ENGLAND JOURNAL of MEDICINE

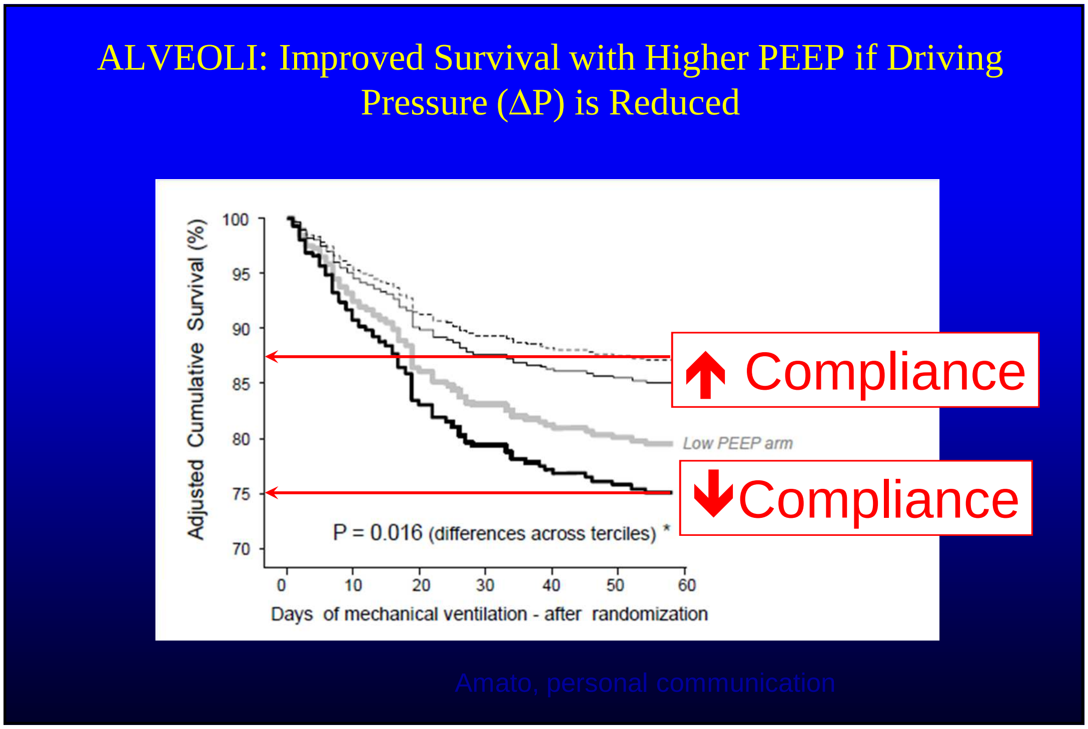
ESTABLISHED IN 1812 JULY 22, 2004 VOL. 351 NO. 4

Higher versus Lower Positive End-Expiratory Pressures
in Patients with the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*



Lower-PEEP group														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher-PEEP group (before protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22–24	
Higher-PEEP group (after protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22–24				

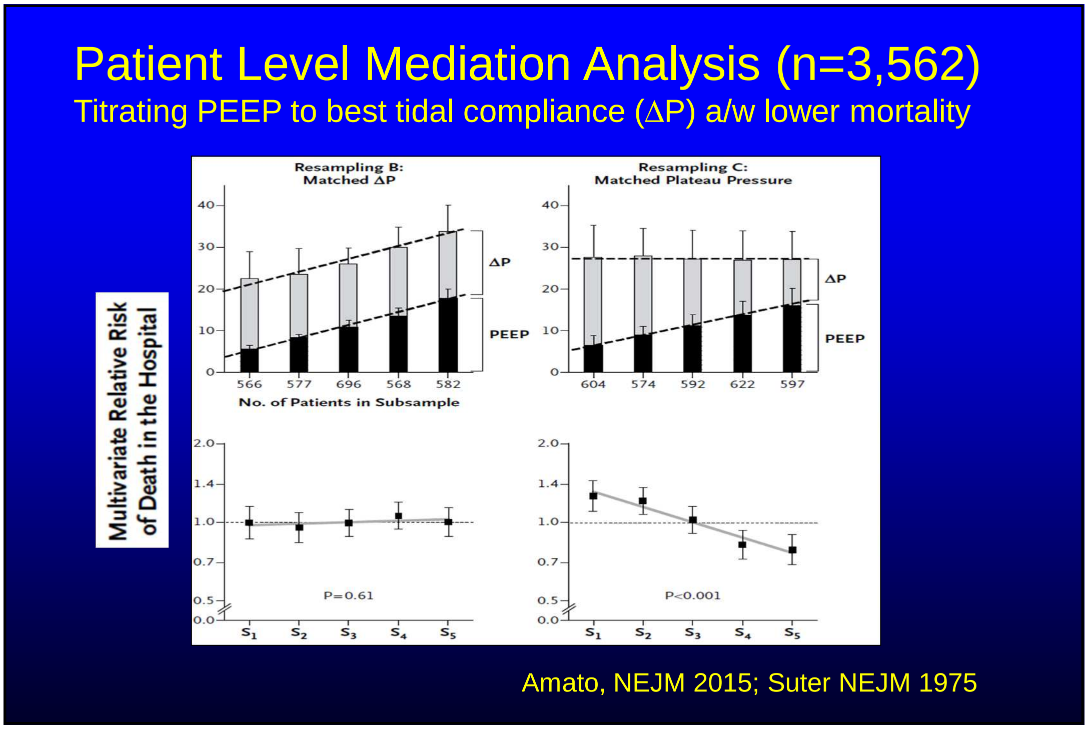


ALVEOLI: Improved Survival with Higher PEEP if Driving Pressure (ΔP) is Reduced

↑ Compliance

↓Compliance

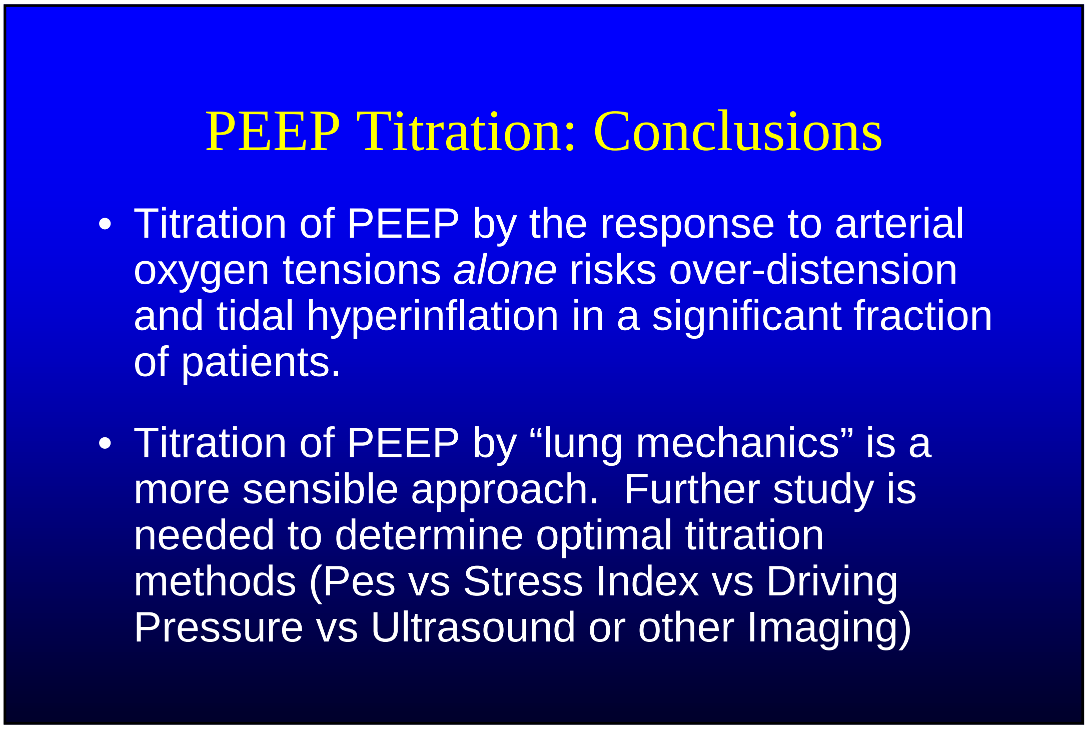
Amato, personal communication



Patient Level Mediation Analysis (n=3,562)

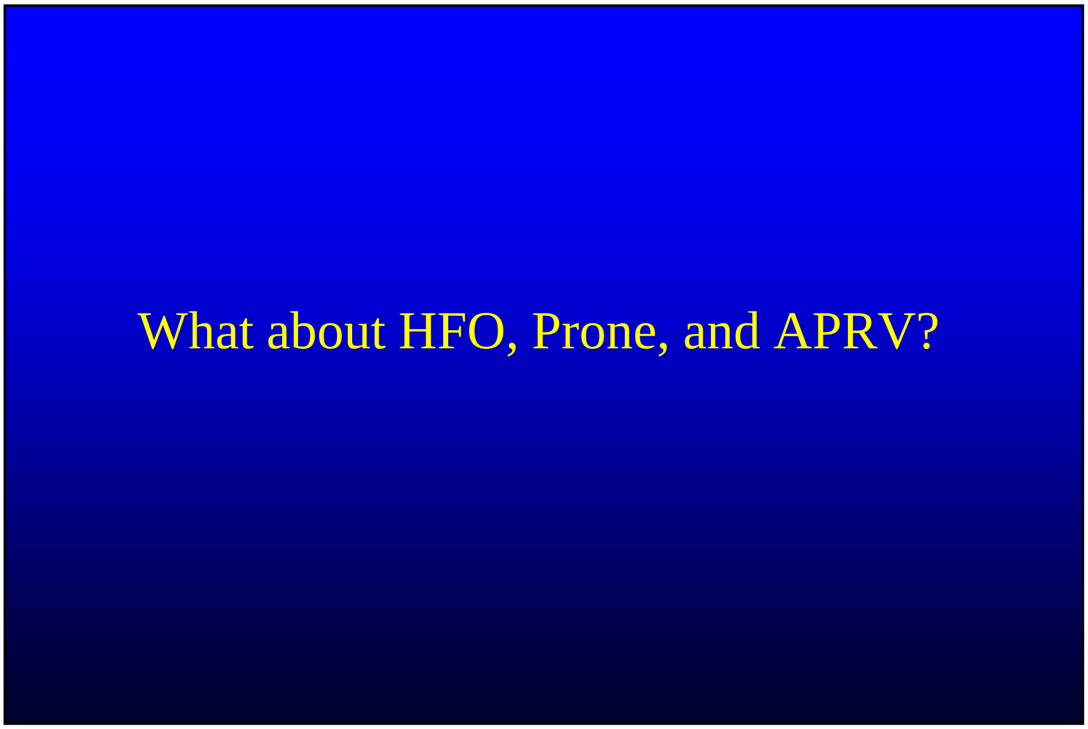
Titrating PEEP to best tidal compliance (ΔP) a/w lower mortality

Amato, NEJM 2015; Suter NEJM 1975

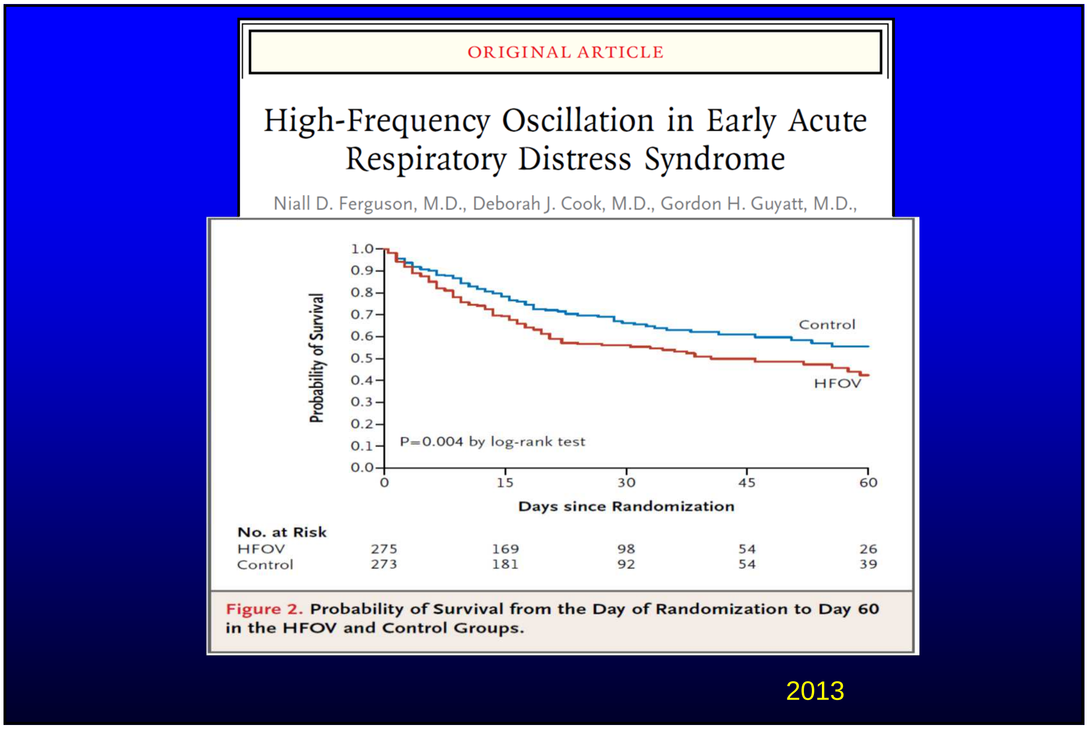


PEEP Titration: Conclusions

- Titration of PEEP by the response to arterial oxygen tensions *alone* risks over-distension and tidal hyperinflation in a significant fraction of patients.
- Titration of PEEP by “lung mechanics” is a more sensible approach. Further study is needed to determine optimal titration methods (Pes vs Stress Index vs Driving Pressure vs Ultrasound or other Imaging)



What about HFO, Prone, and APRV?



ORIGINAL ARTICLE

High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome

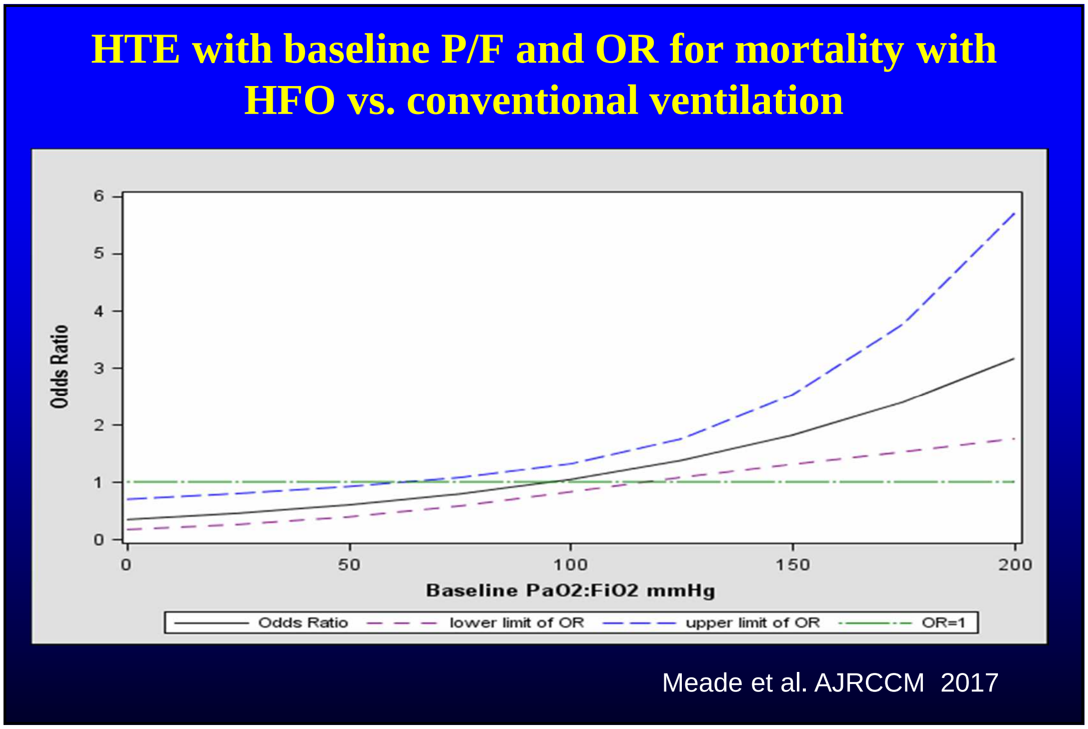
Niall D. Ferguson, M.D., Deborah J. Cook, M.D., Gordon H. Guyatt, M.D.,

No. at Risk

	0	15	30	45	60
HFOV	275	169	98	54	26
Control	273	181	92	54	39

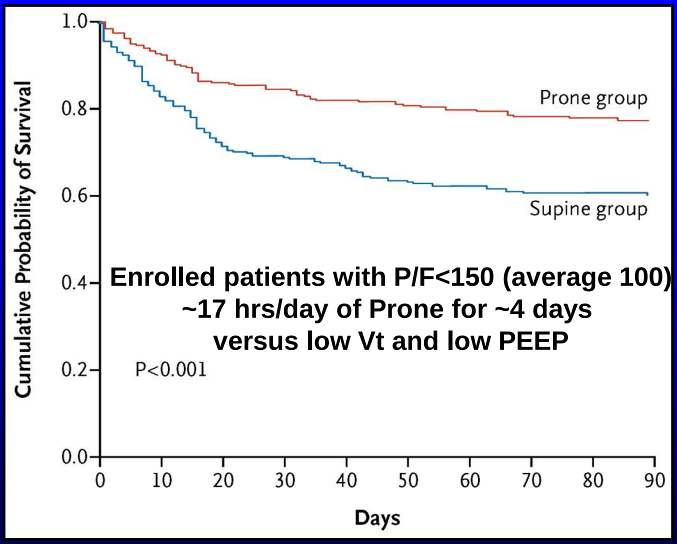
Figure 2. Probability of Survival from the Day of Randomization to Day 60 in the HFOV and Control Groups.

2013



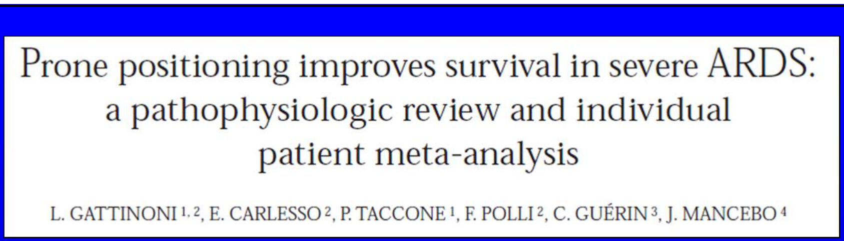
HTE with baseline P/F and OR for mortality with HFO vs. conventional ventilation

Meade et al. AJRCCM 2017



Enrolled patients with P/F<150 (average 100)
~17 hrs/day of Prone for ~4 days
versus low Vt and low PEEP

Guerin NEJM 2013



Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis

L. GATTINONI [1,2], E. CARLESSO [2], P. TACCONE [1], F. POLLI [2], C. GUÉRIN [3], J. MANCEBO [4]

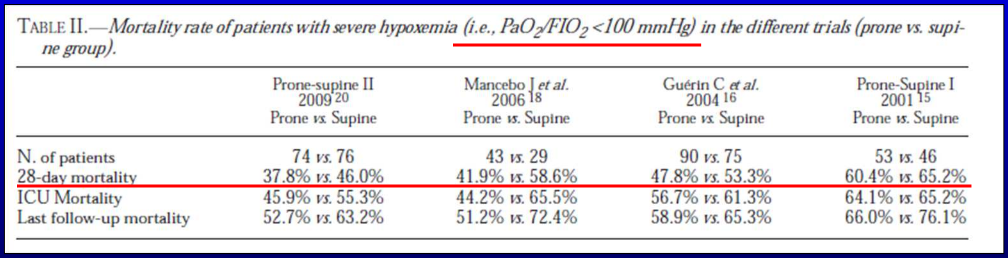
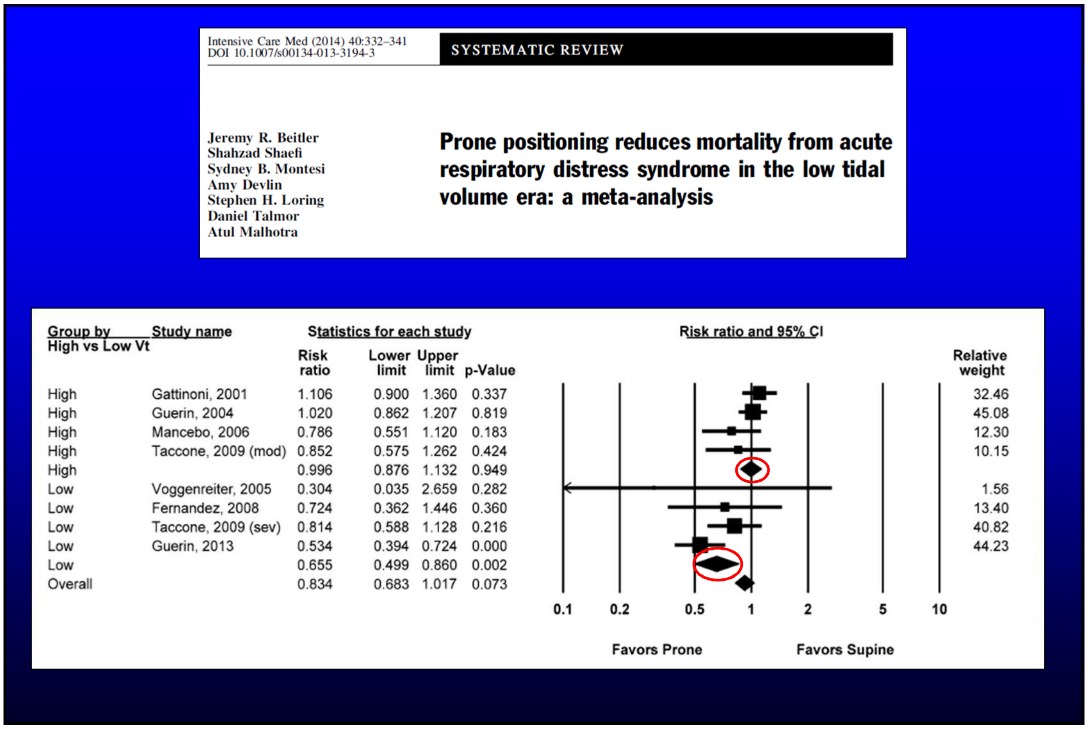


TABLE II.—*Mortality rate of patients with severe hypoxemia (i.e., $PaO_2/FIO_2 < 100$ mmHg) in the different trials (prone vs. supine group).*

	Prone-supine II 2009 [20] Prone *vs.* Supine	Mancebo J *et al.* 2006 [18] Prone *vs.* Supine	Guérin C *et al.* 2004 [16] Prone *vs.* Supine	Prone-Supine I 2001 [15] Prone *vs.* Supine
N. of patients	74 *vs.* 76	43 *vs.* 29	90 *vs.* 75	53 *vs.* 46
28-day mortality	37.8% *vs.* 46.0%	41.9% *vs.* 58.6%	47.8% *vs.* 53.3%	60.4% *vs.* 65.2%
ICU Mortality	45.9% *vs.* 55.3%	44.2% *vs.* 65.5%	56.7% *vs.* 61.3%	64.1% *vs.* 65.2%
Last follow-up mortality	52.7% *vs.* 63.2%	51.2% *vs.* 72.4%	58.9% *vs.* 65.3%	66.0% *vs.* 76.1%

Minerva Anestesiologica 2010



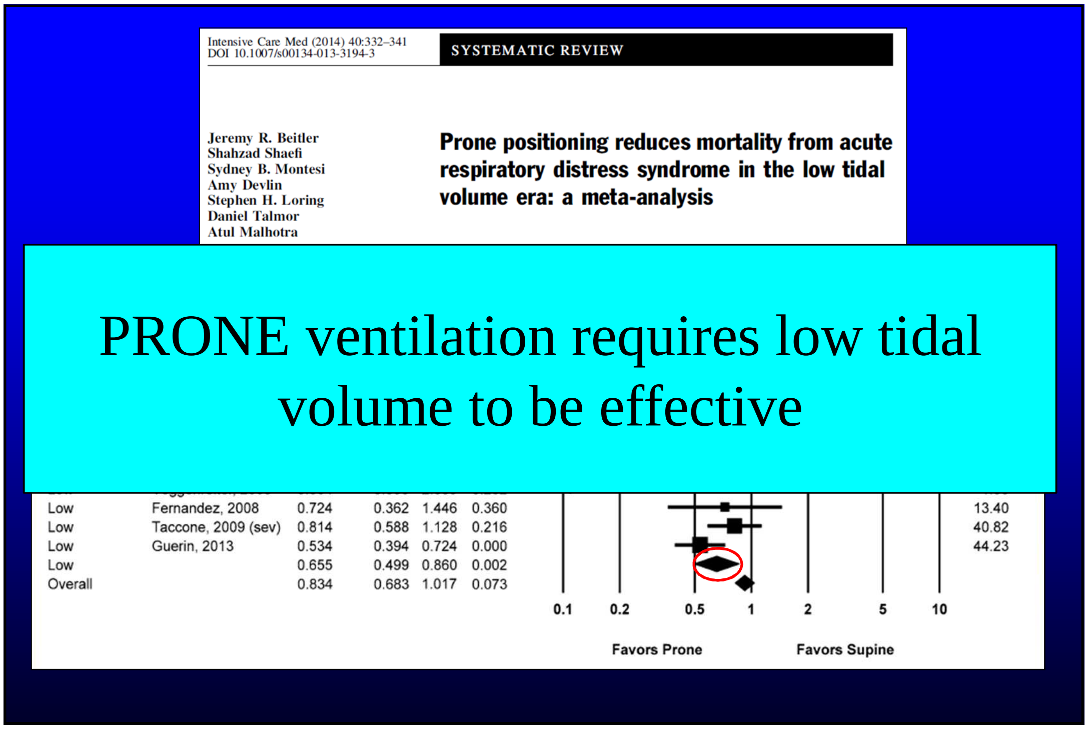
Intensive Care Med (2014) 40:332–341
DOI 10.1007/s00134-013-3194-3

SYSTEMATIC REVIEW

Jeremy R. Beitler
Shahzad Shaefi
Sydney B. Montesi
Amy Devlin
Stephen H. Loring
Daniel Talmor
Atul Malhotra

Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis

Group by High vs Low Vt	Study name	Risk ratio	Lower limit	Upper limit	p-Value	Relative weight
High	Gattinoni, 2001	1.106	0.900	1.360	0.337	32.46
High	Guerin, 2004	1.020	0.862	1.207	0.819	45.08
High	Mancebo, 2006	0.786	0.551	1.120	0.183	12.30
High	Taccone, 2009 (mod)	0.852	0.575	1.262	0.424	10.15
High		0.996	0.876	1.132	0.949	
Low	Voggenreiter, 2005	0.304	0.035	2.659	0.282	1.56
Low	Fernandez, 2008	0.724	0.362	1.446	0.360	13.40
Low	Taccone, 2009 (sev)	0.814	0.588	1.128	0.216	40.82
Low	Guerin, 2013	0.534	0.394	0.724	0.000	44.23
Low		0.655	0.499	0.860	0.002	
Overall		0.834	0.683	1.017	0.073	



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Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis

PRONE ventilation requires low tidal volume to be effective

Low	Fernandez, 2008	0.724	0.362	1.446	0.360	13.40
Low	Taccone, 2009 (sev)	0.814	0.588	1.128	0.216	40.82
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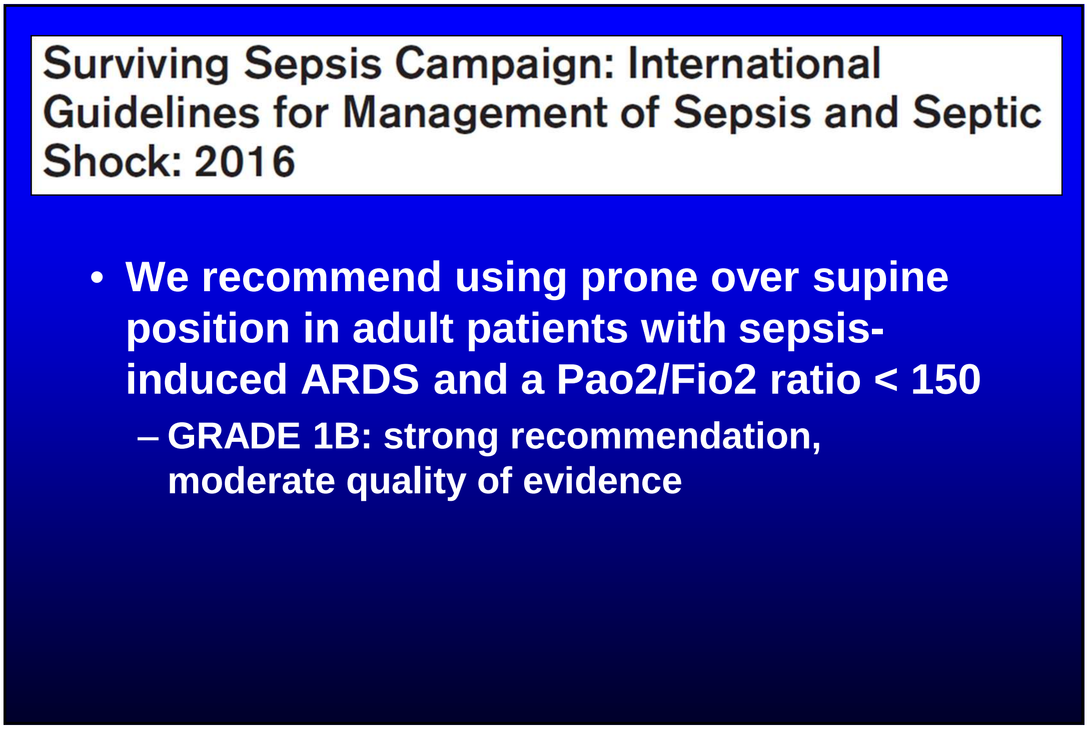
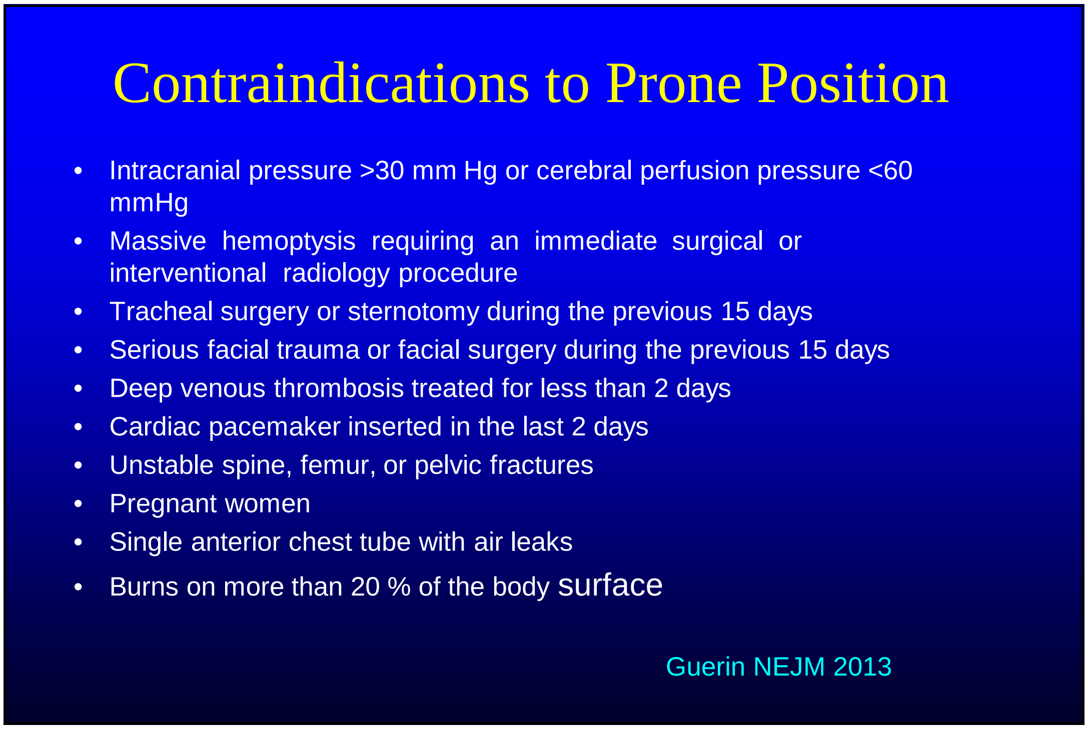


Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

- We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a Pao2/Fio2 ratio < 150
  - GRADE 1B: strong recommendation, moderate quality of evidence

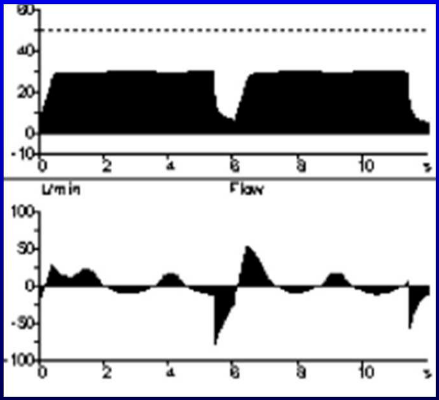


Contraindications to Prone Position

- Intracranial pressure >30 mm Hg or cerebral perfusion pressure <60 mmHg
- Massive hemoptysis requiring an immediate surgical or interventional radiology procedure
- Tracheal surgery or sternotomy during the previous 15 days
- Serious facial trauma or facial surgery during the previous 15 days
- Deep venous thrombosis treated for less than 2 days
- Cardiac pacemaker inserted in the last 2 days
- Unstable spine, femur, or pelvic fractures
- Pregnant women
- Single anterior chest tube with air leaks
- Burns on more than 20 % of the body surface

Guerin NEJM 2013

Airway Pressure Release Ventilation



- Improved hemodynamics, reduced intrapulmonary shunt, reduced sedative requirements versus PCV
- Concerns:
  - Level of airway pressure and resulting large “release volumes”
  - Intermittent de-recruitment
- RCTs needed

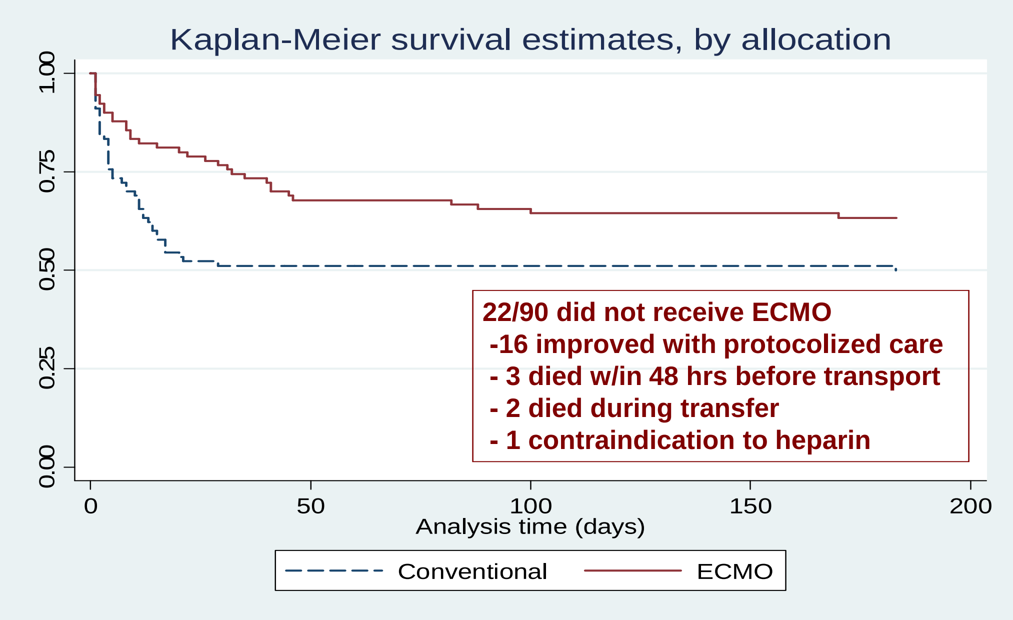
Kaplan et al CCM 2001

CESAR

Conventional ventilatory support versus
Extracorporeal membrane oxygenation for
Severe
Adult
Respiratory failure

a multicentre randomized controlled trial

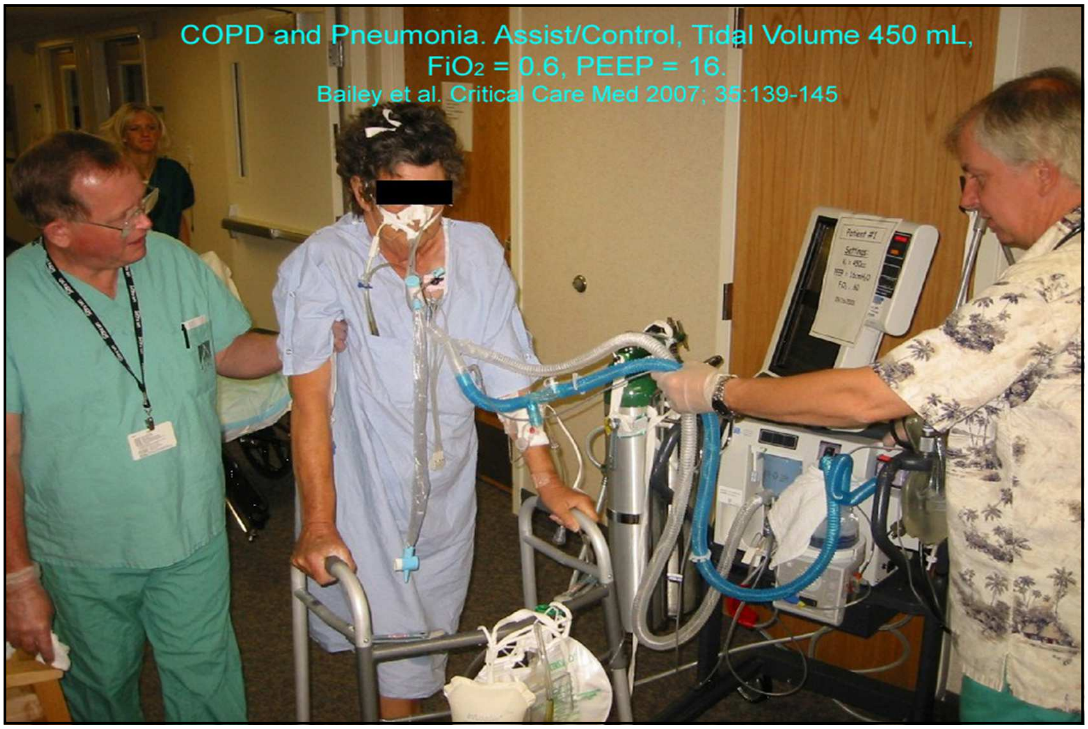
Lancet 2009; 374: 1351-63



22/90 did not receive ECMO
- **16 improved with protocolized care**
- **3 died w/in 48 hrs before transport**
- **2 died during transfer**
- **1 contraindication to heparin**

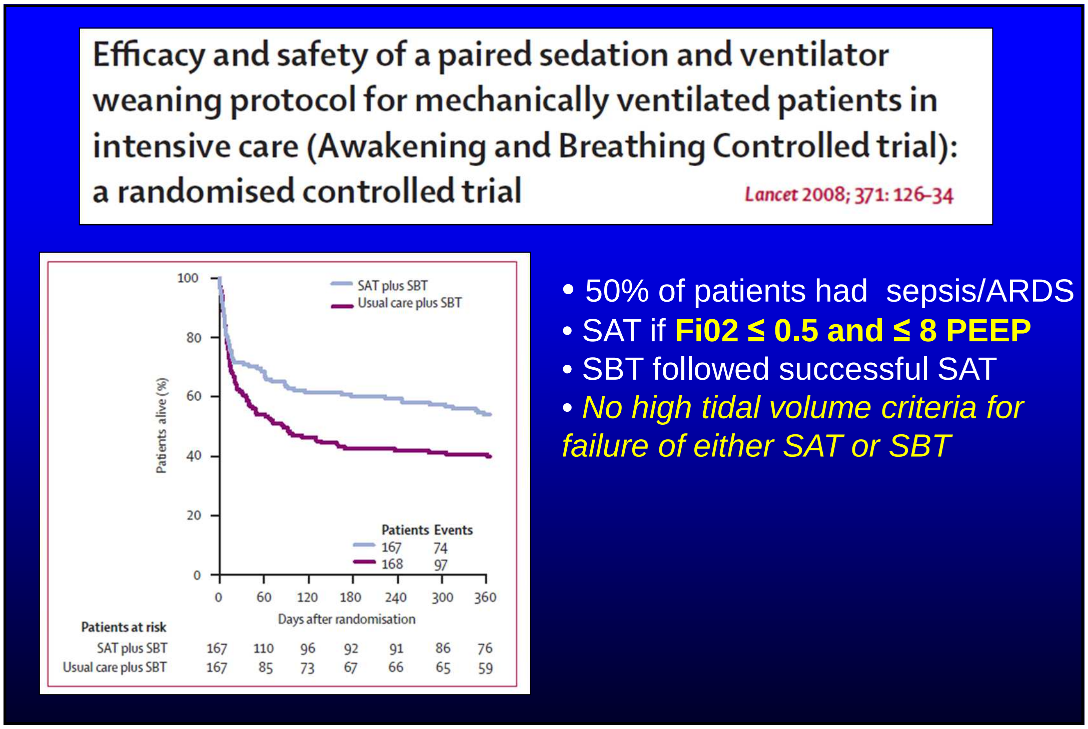
Peek et al Lancet 2009

When should we allow spontaneous respiratory efforts in patients with ARDS?



COPD and Pneumonia. Assist/Control, Tidal Volume 450 mL, FiO$_2$ = 0.6, PEEP = 16.

Bailey et al. Critical Care Med 2007; 35:139-145

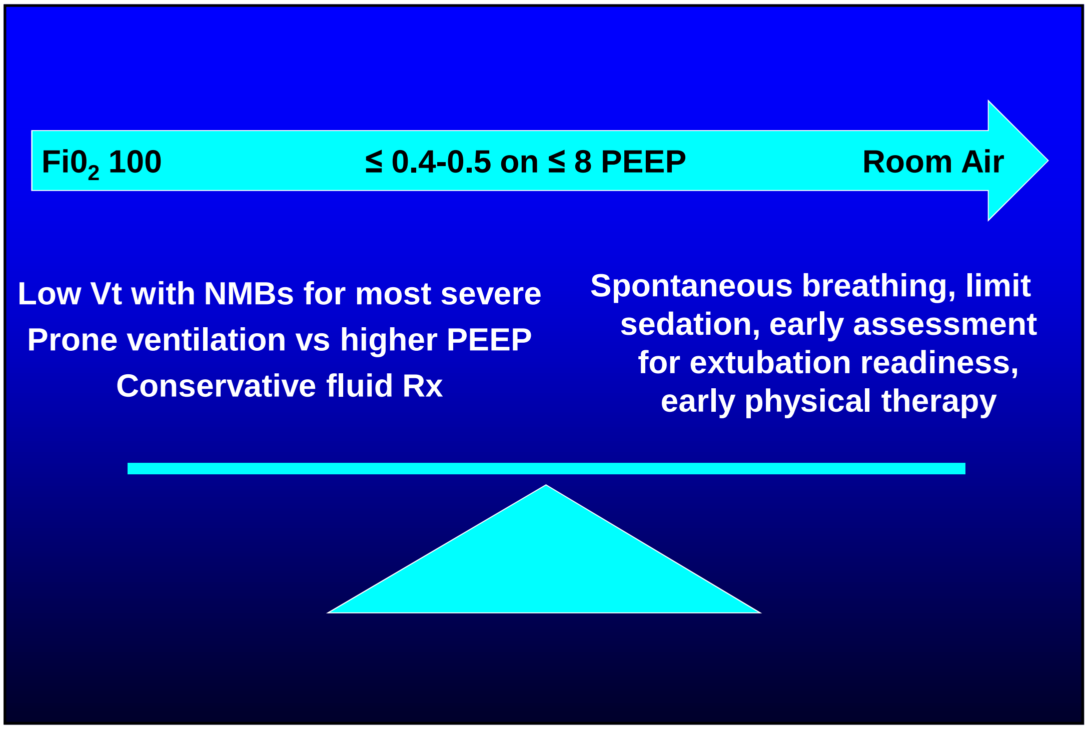


Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

Lancet 2008; 371: 126–34

Patients at risk							
SAT plus SBT	167	110	96	92	91	86	76
Usual care plus SBT	167	85	73	67	66	65	59

- 50% of patients had sepsis/ARDS
- SAT if **Fi02 ≤ 0.5 and ≤ 8 PEEP**
- SBT followed successful SAT
- *No high tidal volume criteria for failure of either SAT or SBT*



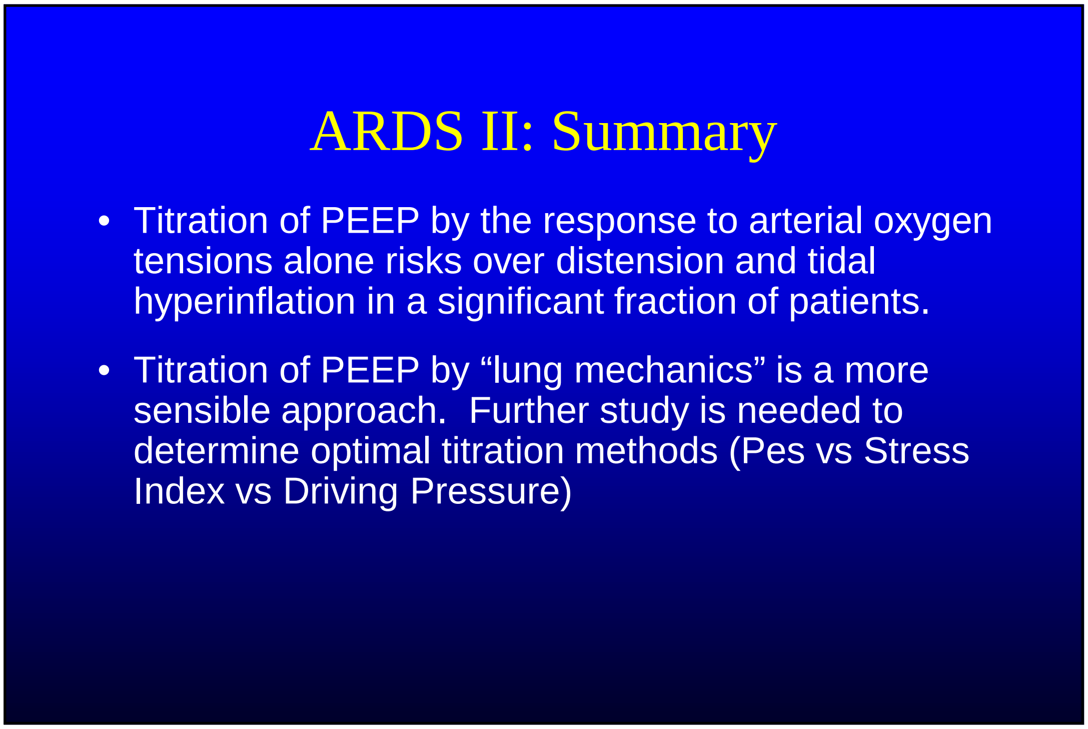
FiO_2 100 → ≤ 0.4-0.5 on ≤ 8 PEEP → Room Air

Low Vt with NMBs for most severe
Prone ventilation vs higher PEEP
Conservative fluid Rx

Spontaneous breathing, limit sedation, early assessment for extubation readiness, early physical therapy

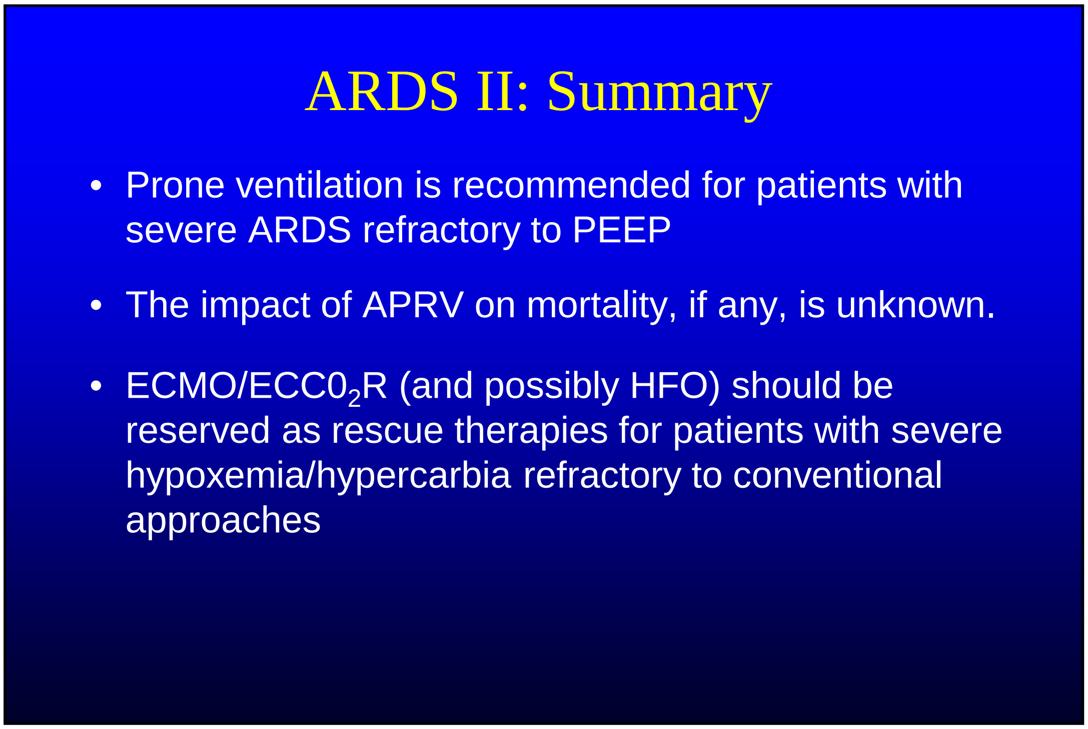
ARDS II: Summary

- Low tidal volume ventilation is a safe and effective treatment for ARDS
- The safe level of transpulmonary pressure, if any, in patients with lung injury is unknown and volu/biotrauma may be occurring at airway pressures previously assumed to be safe.



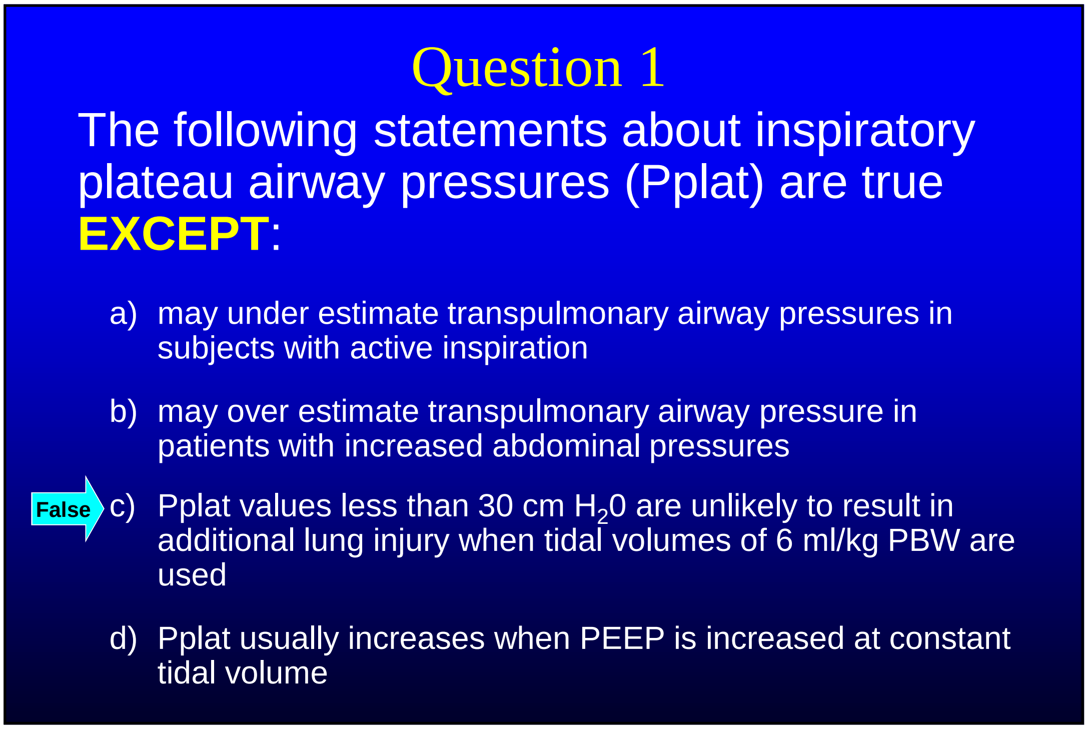
ARDS II: Summary

- Titration of PEEP by the response to arterial oxygen tensions alone risks over distension and tidal hyperinflation in a significant fraction of patients.
- Titration of PEEP by "lung mechanics" is a more sensible approach. Further study is needed to determine optimal titration methods (Pes vs Stress Index vs Driving Pressure)



ARDS II: Summary

- Prone ventilation is recommended for patients with severe ARDS refractory to PEEP
- The impact of APRV on mortality, if any, is unknown.
- ECMO/ECC0$_2$R (and possibly HFO) should be reserved as rescue therapies for patients with severe hypoxemia/hypercarbia refractory to conventional approaches



Question 1

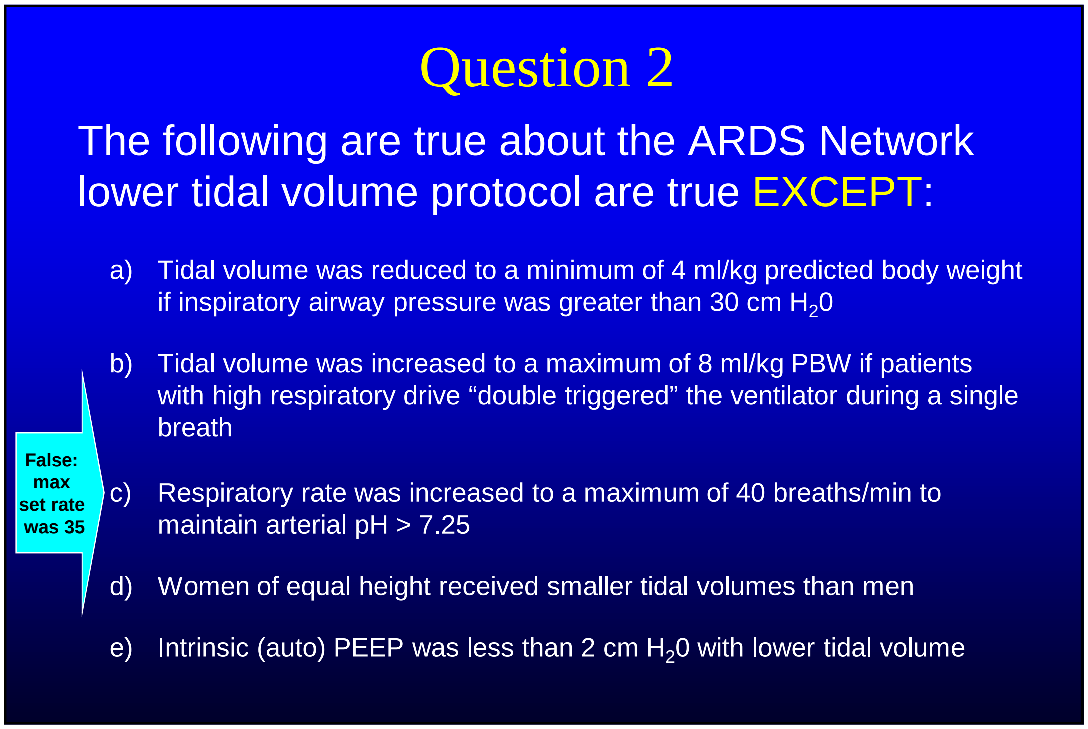
The following statements about inspiratory plateau airway pressures (Pplat) are true **EXCEPT**:

a) may under estimate transpulmonary airway pressures in subjects with active inspiration

b) may over estimate transpulmonary airway pressure in patients with increased abdominal pressures

False c) Pplat values less than 30 cm H$_2$0 are unlikely to result in additional lung injury when tidal volumes of 6 ml/kg PBW are used

d) Pplat usually increases when PEEP is increased at constant tidal volume



Question 2

The following are true about the ARDS Network lower tidal volume protocol are true EXCEPT:

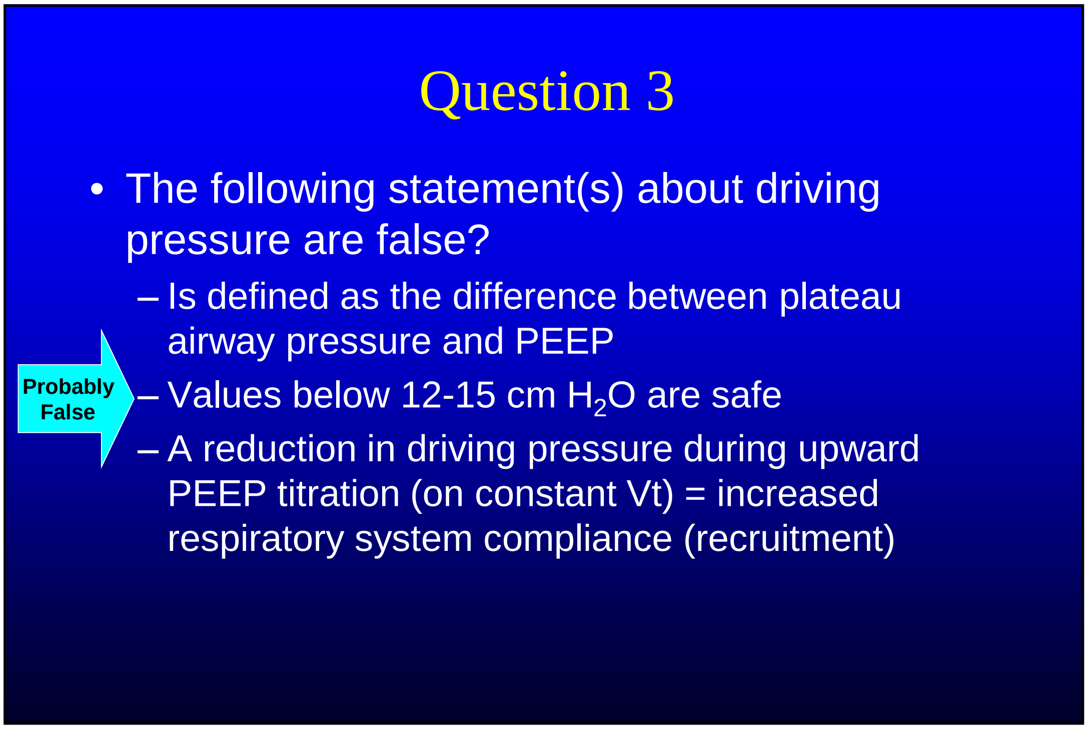
a) Tidal volume was reduced to a minimum of 4 ml/kg predicted body weight if inspiratory airway pressure was greater than 30 cm H$_2$0

b) Tidal volume was increased to a maximum of 8 ml/kg PBW if patients with high respiratory drive “double triggered” the ventilator during a single breath

False: max set rate was 35 c) Respiratory rate was increased to a maximum of 40 breaths/min to maintain arterial pH > 7.25

d) Women of equal height received smaller tidal volumes than men

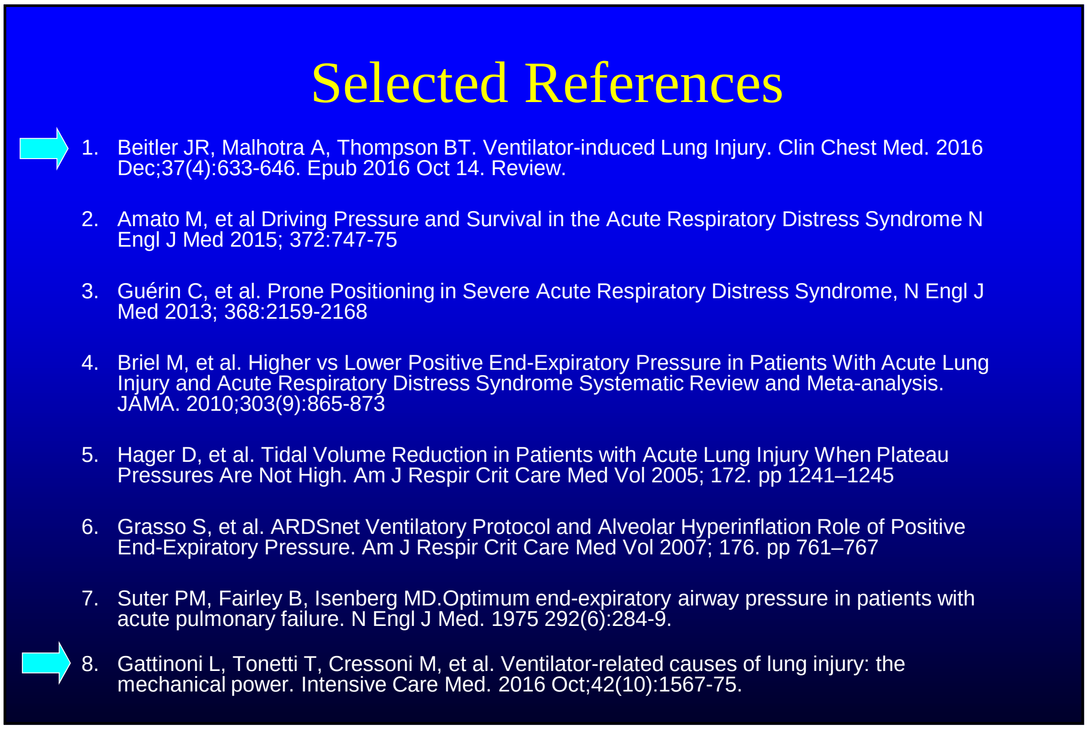
e) Intrinsic (auto) PEEP was less than 2 cm H$_2$0 with lower tidal volume



Question 3

- The following statement(s) about driving pressure are false?
  - Is defined as the difference between plateau airway pressure and PEEP
  - Values below 12-15 cm H_2O are safe
  - A reduction in driving pressure during upward PEEP titration (on constant Vt) = increased respiratory system compliance (recruitment)

Probably False



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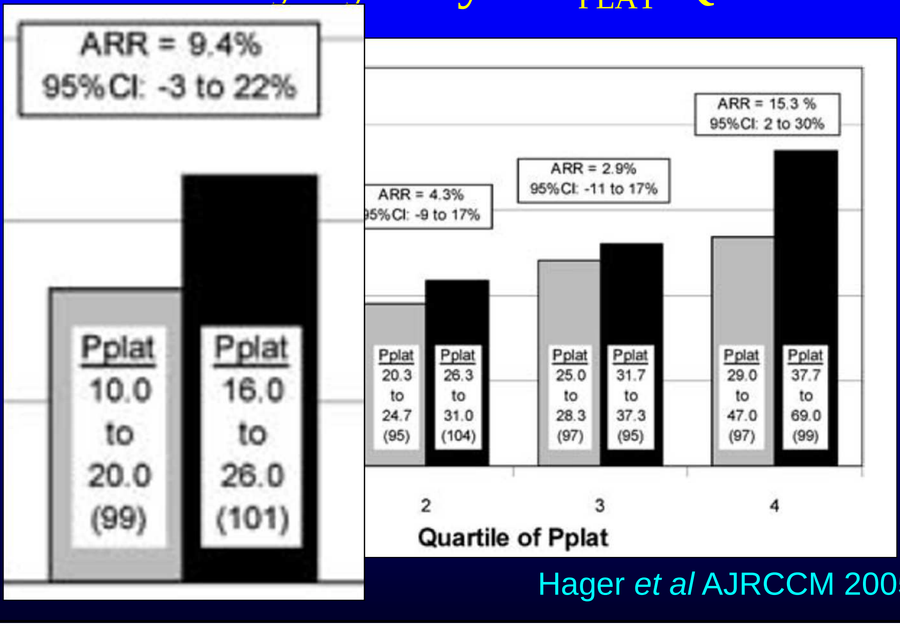
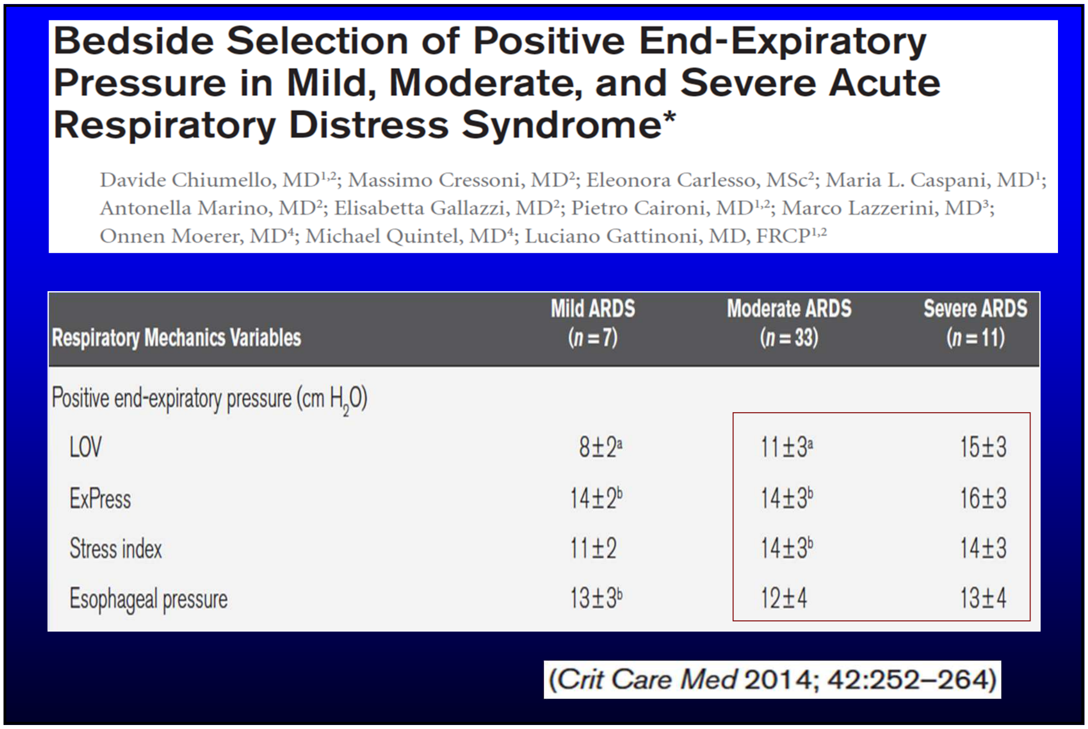
1. ➡ Beitler JR, Malhotra A, Thompson BT. Ventilator-induced Lung Injury. Clin Chest Med. 2016 Dec;37(4):633-646. Epub 2016 Oct 14. Review.
2. Amato M, et al Driving Pressure and Survival in the Acute Respiratory Distress Syndrome N Engl J Med 2015; 372:747-75
3. Guérin C, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome, N Engl J Med 2013; 368:2159-2168
4. Briel M, et al. Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome Systematic Review and Meta-analysis. JAMA. 2010;303(9):865-873
5. Hager D, et al. Tidal Volume Reduction in Patients with Acute Lung Injury When Plateau Pressures Are Not High. Am J Respir Crit Care Med Vol 2005; 172. pp 1241–1245
6. Grasso S, et al. ARDSnet Ventilatory Protocol and Alveolar Hyperinflation Role of Positive End-Expiratory Pressure. Am J Respir Crit Care Med Vol 2007; 176. pp 761–767
7. Suter PM, Fairley B, Isenberg MD.Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med. 1975 292(6):284-9.
8. ➡ Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med. 2016 Oct;42(10):1567-75.

Thank you

Mortality by Day 1 P_{PLAT} Quartiles



Hager *et al* AJRCCM 2005

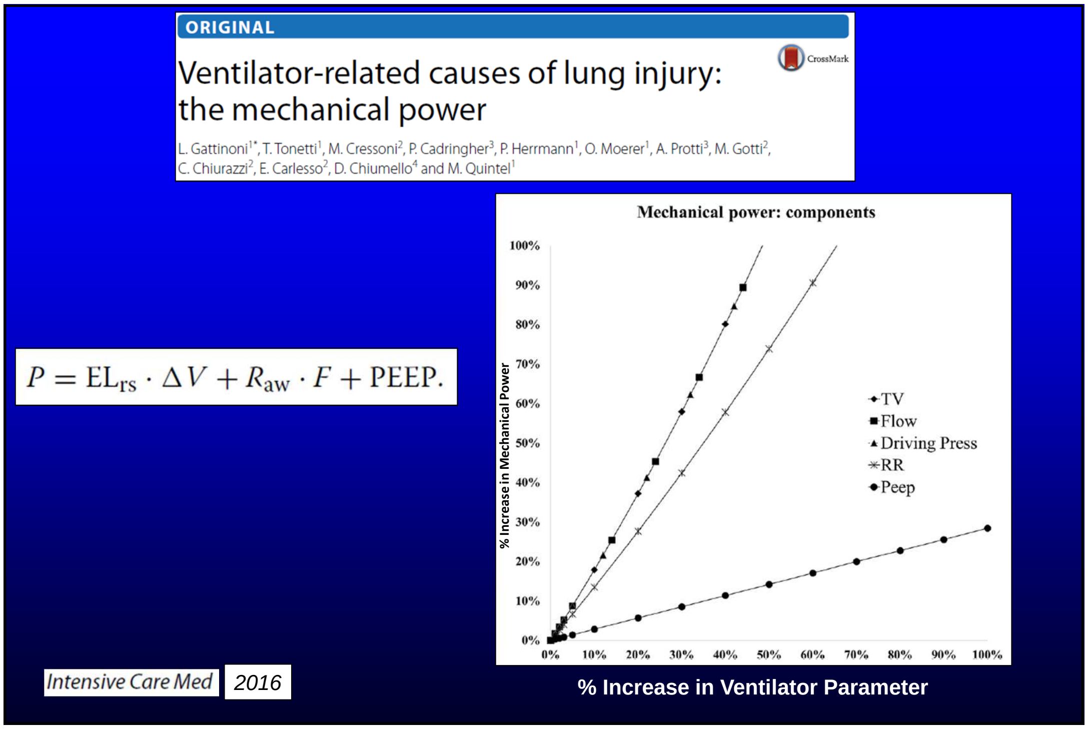


Bedside Selection of Positive End-Expiratory Pressure in Mild, Moderate, and Severe Acute Respiratory Distress Syndrome*

Davide Chiumello, MD[1,2]; Massimo Cressoni, MD[2]; Eleonora Carlesso, MSc[2]; Maria L. Caspani, MD[1]; Antonella Marino, MD[2]; Elisabetta Gallazzi, MD[2]; Pietro Caironi, MD[1,2]; Marco Lazzerini, MD[3]; Onnen Moerer, MD[4]; Michael Quintel, MD[4]; Luciano Gattinoni, MD, FRCP[1,2]

Respiratory Mechanics Variables	Mild ARDS (*n* = 7)	Moderate ARDS (*n* = 33)	Severe ARDS (*n* = 11)
Positive end-expiratory pressure (cm H_2O)			
LOV	8±2[a]	11±3[a]	15±3
ExPress	14±2[b]	14±3[b]	16±3
Stress index	11±2	14±3[b]	14±3
Esophageal pressure	13±3[b]	12±4	13±4

(*Crit Care Med* 2014; 42:252–264)



ORIGINAL

Ventilator-related causes of lung injury: the mechanical power

L. Gattinoni[1*], T. Tonetti[1], M. Cressoni[2], P. Cadringher[3], P. Herrmann[1], O. Moerer[1], A. Protti[3], M. Gotti[2], C. Chiurazzi[2], E. Carlesso[2], D. Chiumello[4] and M. Quintel[1]

$$P = EL_{rs} \cdot \Delta V + R_{aw} \cdot F + PEEP.$$

Mechanical power: components

% Increase in Ventilator Parameter

Intensive Care Med 2016

COPD:
A Preventable and Treatable Disease

Bartolome R. Celli, M.D.
Brigham and Women’s Hospital
Professor of Medicine
Harvard Medical School

B. Celli Disclaimer

No stocks or ownership in any company.

No Tobacco funds

Grants: ***GSK , B.I., Amgen, Novartis, Forrest, Astra Zeneca***

Advisory boards: ***GSK, B.I., Astra Zeneca, Novartis, Cipla.***

Objective

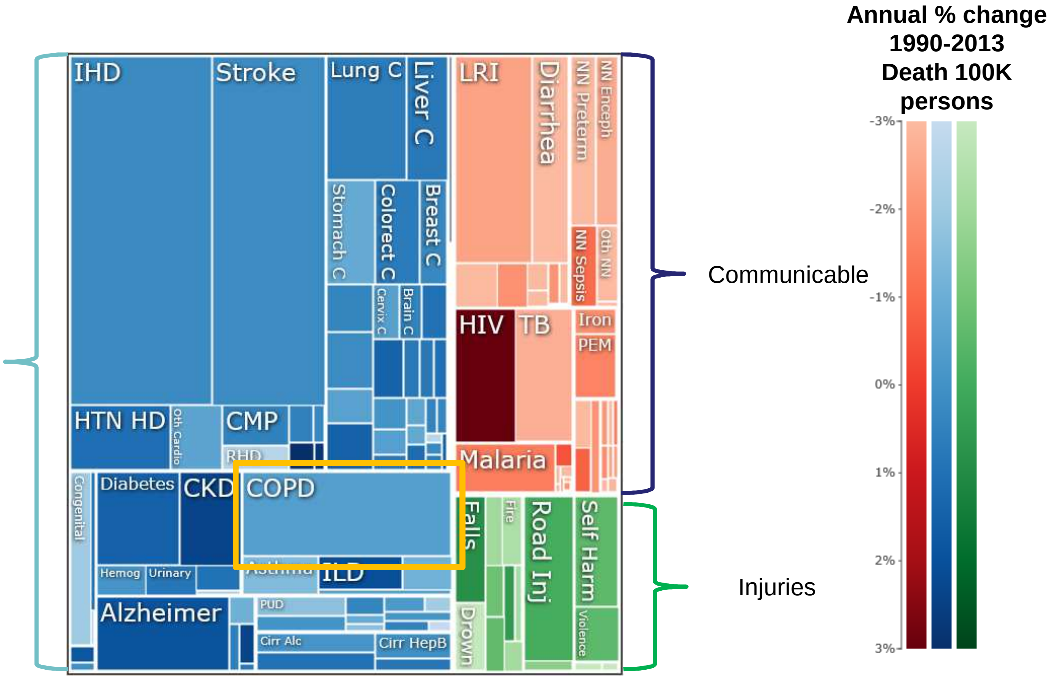
- A big problem that progresses over a long period of time
- Patients respond to therapy
- Bronchodilators
- Anti-inflammatories
- New agents
- A logical approach

Objective

- A big problem

www.GBD
Accessed
4/2017

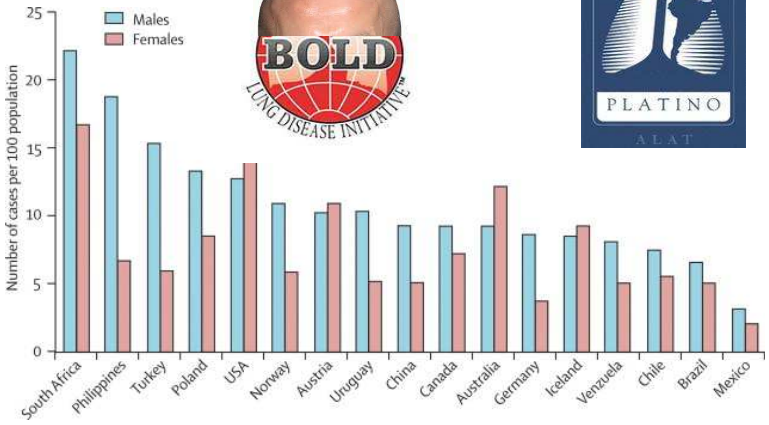
Non
Communicable



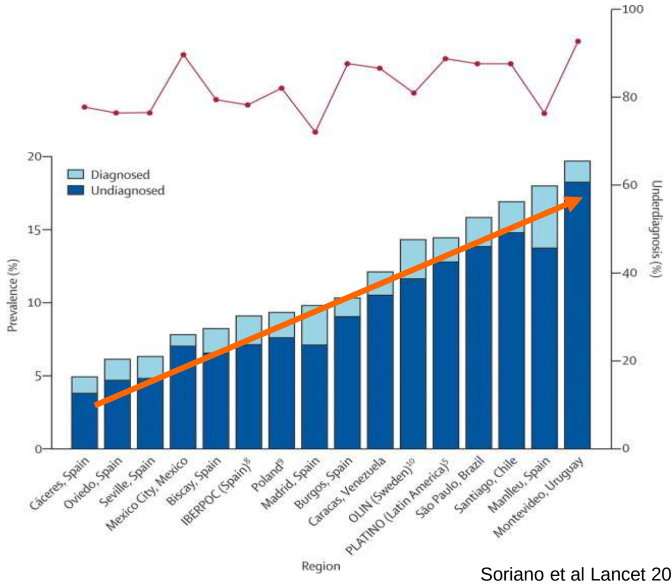
Prevalence of COPD

BOLD
LUNG DISEASE INITIATIVE

PLATINO
ALAT



Underdiagnosis in COPD

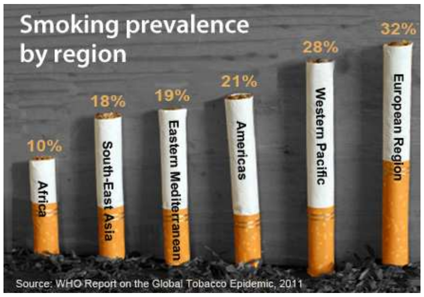


Soriano et al Lancet 2009;721

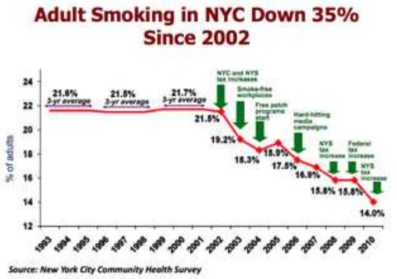
Which of these is true of COPD

A. Is invariable progressive
B. Does respond to pharmacotherapy
C. Exacerbations are rare and cause little problems
D. Is difficult to diagnose

Smoking: still a problem



Source: WHO Report on the Global Tobacco Epidemic, 2011



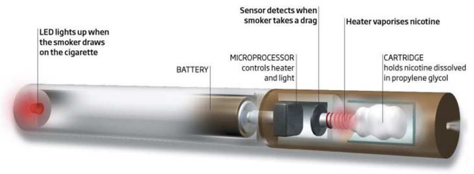
Source: New York City Community Health Survey

E cigarettes

TRY E-CIGARETTES
QUIT SMOKING & SATISFY YOUR CRAVING!
No Tar or Carbon Monoxide
No Ash, Stub or Terrible Smell
No Yellow Teeth or Bad Breath
Virtually Odorless
Same Nicotine Fix, Real Vapor
Less Harmful To Yourself & Others
CLICK HERE...
GET YOURS TODAY!
E-Cigs

Vaping

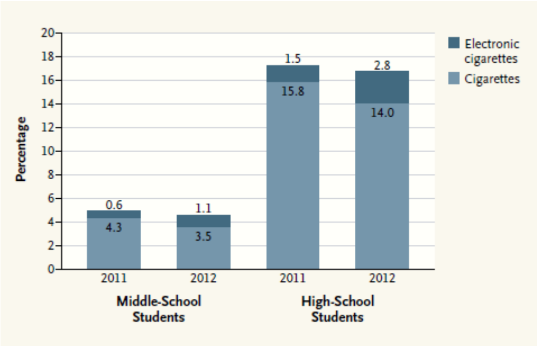
Upon inhalation the heater known as the atomiser vaporises the nicotine solution turning it into vapour. The user in turn inhales this to get the similar nicotine hit as a normal cigarette, and a real smoking satisfaction.

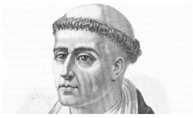

Sensor detects when smoker takes a drag
Heater vaporises nicotine
LED lights up when the smoker draws on the cigarette
BATTERY
MICROPROCESSOR controls heater and light
CARTRIDGE holds nicotine dissolved in propylene glycol

Sales in USA in 2013 $ 1 billion

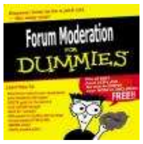
The NEW ENGLAND JOURNAL of MEDICINE

The Renormalization of Smoking? E-Cigarettes and the Tobacco “Endgame”





Zealots


Forum Moderation
FOR
DUMMIES

Moderates

Objective

- Progresses over a long period of time

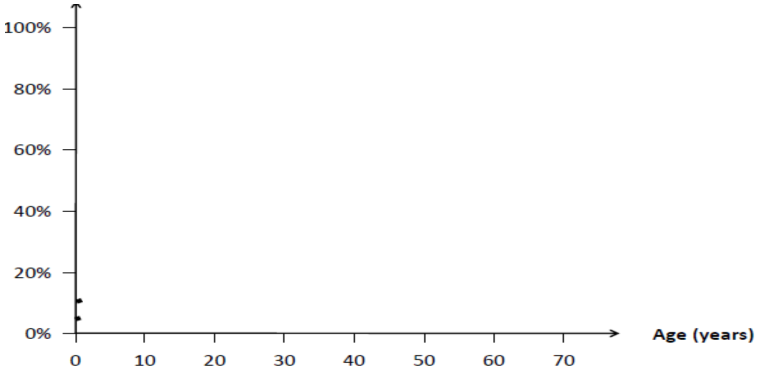
BC1

Baseline FEV_1 and development of GOLD II COPD

FOC

LSC

CCH



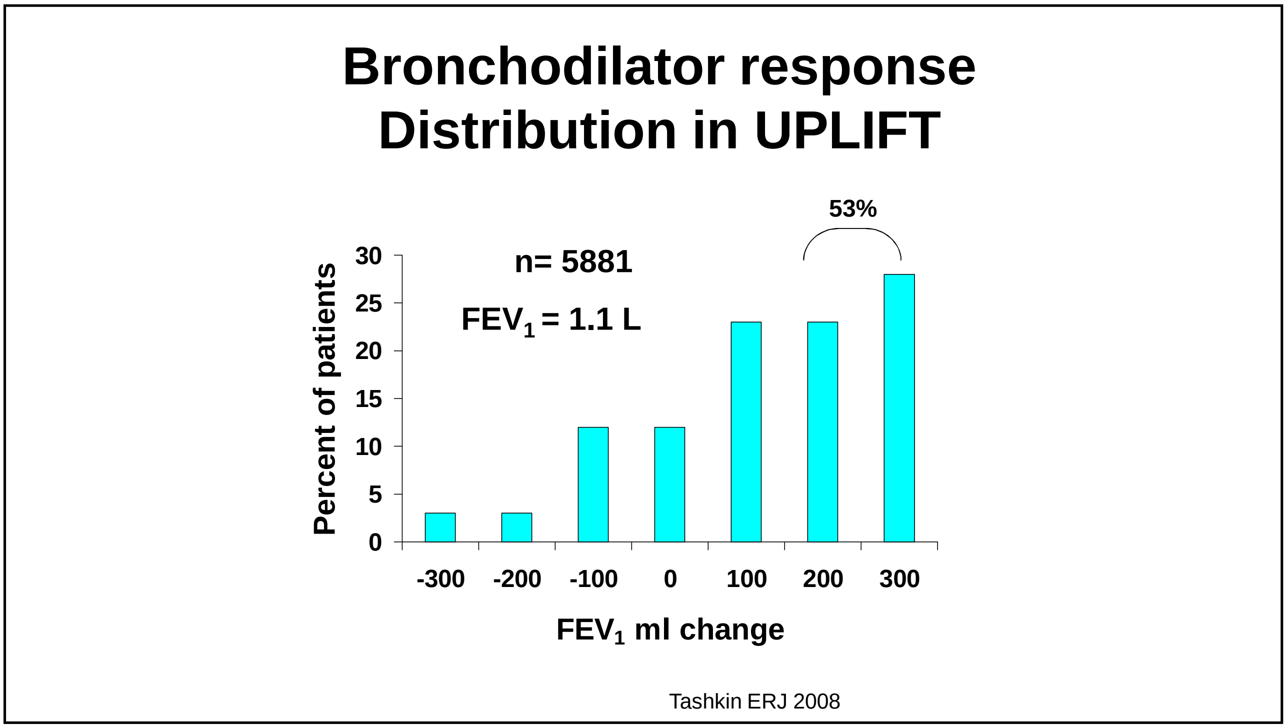
Lange P et al NEJM 2015;372:2

Objective

- Patients respond to therapy

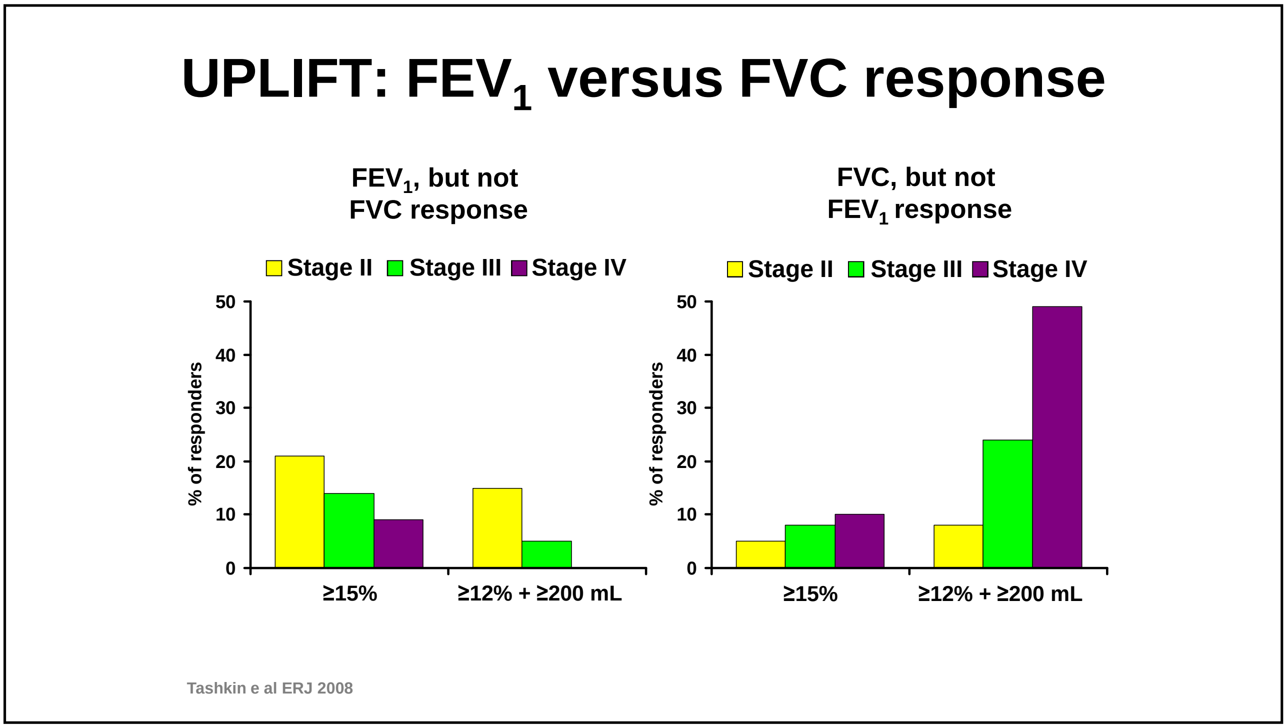
Slide 13

BC1 Bartolome Celli, 4/27/2016



Bronchodilator response Distribution in UPLIFT

Tashkin ERJ 2008

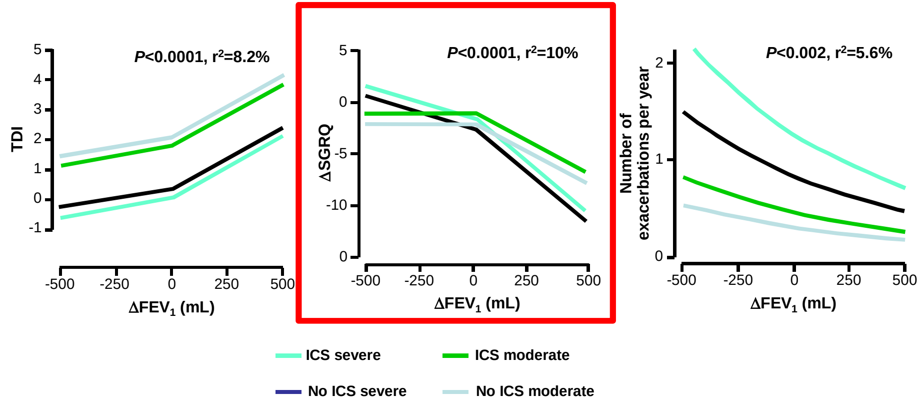


UPLIFT: FEV$_1$ versus FVC response

Tashkin e al ERJ 2008

Benefits of maximal bronchodilation on clinical outcomes

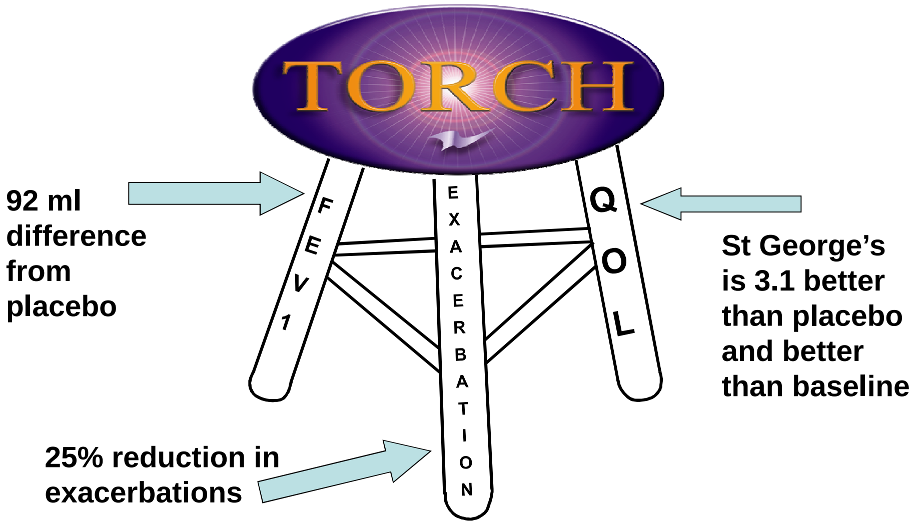
Correlation between change in FEV_1 and outcomes



Correlation analysis of pooled data from three indacaterol studies (N=3313)

Jones PW et al, *Respir Res* 2011;12:161.

TORCH: DB, R, PC, 3 year trial. 6000 patients comparing F, S, SF, P
Outcome: Primary: Mortality Secondary: FEV1, QoL, Exacerbations



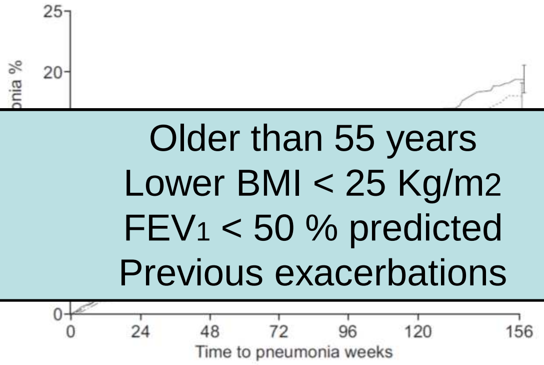
92 ml difference from placebo

St George's is 3.1 better than placebo and better than baseline

25% reduction in exacerbations

Calverley P et al NEJM 2007;22:356

Pneumonia Risk in TORCH

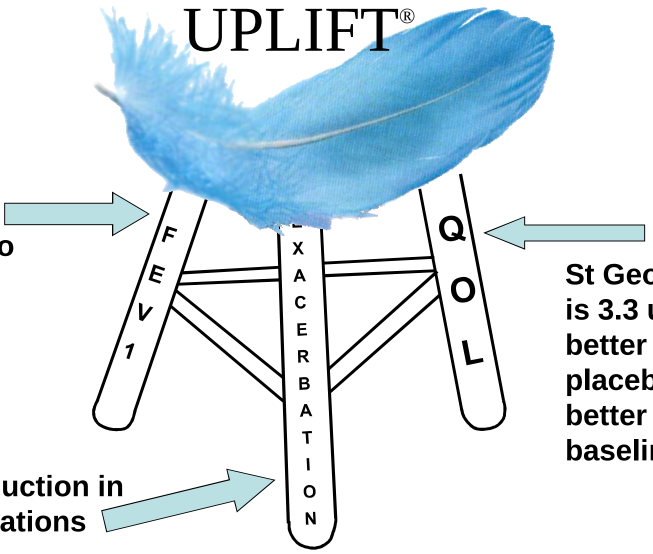


Older than 55 years
Lower BMI < 25 Kg/m2
FEV_1 < 50 % predicted
Previous exacerbations

Patients n				
SFC	1546	1231	1034	631
FP	1552	1189	992	574
SAL	1542	1214	1024	645
P	1544	1117	947	587

Crim C et al ERJ 2009;34:341

UPLIFT: DB, R, PC, 4 year trial. 6000 patients. Tio vs Usual care
Outcome: Primary: FEV1 decline Secondary: QoL, AE, Mortality



110 ml difference from placebo

St George's is 3.3 units better than placebo and better than baseline

16% reduction in exacerbations

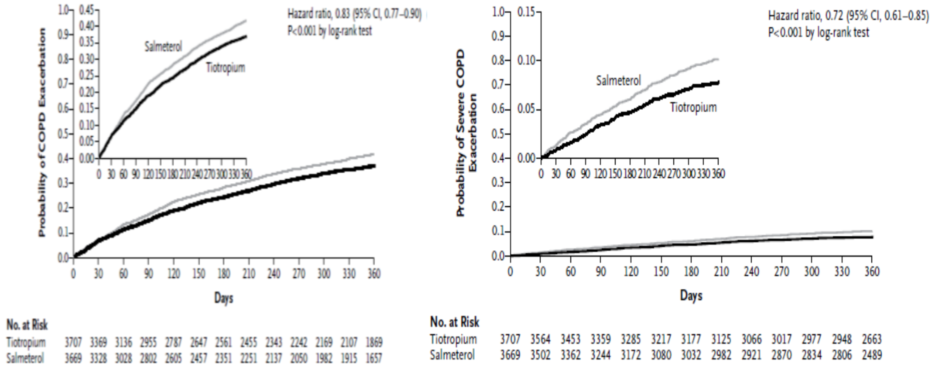
Tashkin D et al NEJM 2008;359:1543

Patients with COPD

A. Respond poorly to pharmacotherapy
B. Are best treated with bed rest and limitations of activities
C. Are usually detected early
D. Rarely exacerbate
E. Frequently improve over time

Salmeterol vs Tiotropium (POET)

N > 7000 patients



No. at Risk													
Tiotropium	3707	3369	3136	2955	2787	2647	2561	2455	2343	2242	2169	2107	1869
Salmeterol	3669	3328	3028	2802	2605	2457	2351	2251	2137	2050	1982	1915	1657

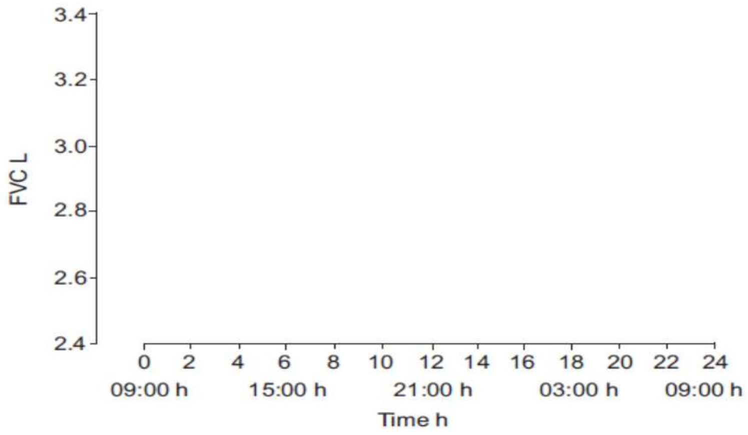
No. at Risk													
Tiotropium	3707	3564	3453	3359	3285	3217	3177	3125	3066	3017	2977	2948	2663
Salmeterol	3669	3502	3362	3244	3172	3080	3032	2982	2921	2870	2834	2806	2489

Vogelmeier et al NEJM 2011;364:1093

Are 2 better than 1?

Comparison Tiotropium (T) versus Formoterol (F) bid and both combined qd

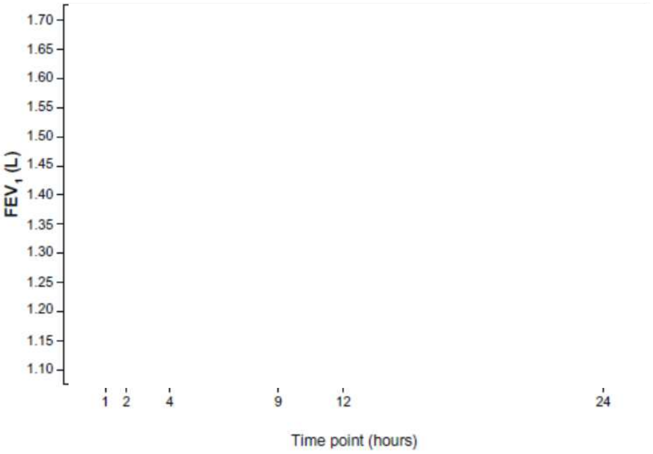
n = 71 FEV1=1.04L Cross-over 3 X 6 weeks periods   T, T+ F qd and F bid



Van Noord J et al ERJ 2005;26:214

Long Acting Muscarinic Agent Umeclidinium + Salmeterol (S) versus S, Tiotropium (T) or Placebo

N = 47 FEV$_1$ = 1.5 L R,PC,Crossover 1 week



Beier J et al Intl J COPD 2012;7:153

Are 3 better than 2?

Tiotropium + (Placebo, Salmeterol, or S/F) in COPD

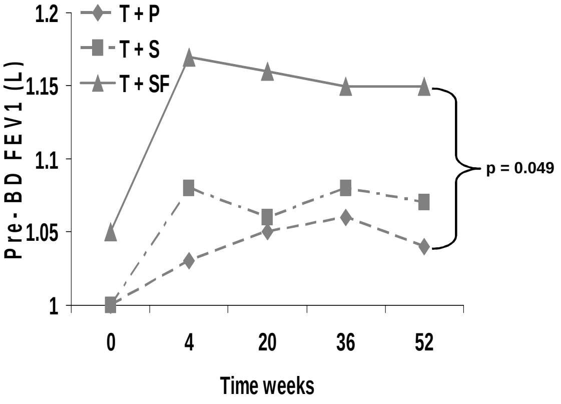
n = 449

1 year

FEV_1 = 1.02 L

Primary Outcome

Exacerbations



Aaron S et al Ann Intern Med 2007;146:545

Tiotropium vs Tio/Bud/Formoterol

n = 660

12 weeks

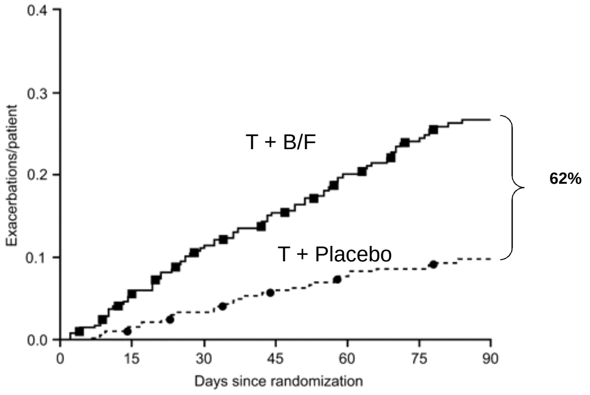
FEV_1 = 1.1 L

Outcome

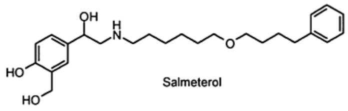
lung function

QoL

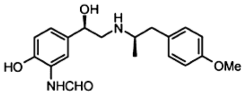
Exacerbations



Welte et al AJRCCM 2009;180:741

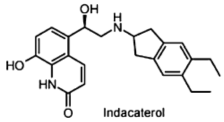


Salmeterol

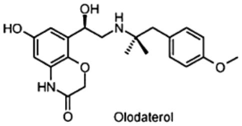


Formoterol

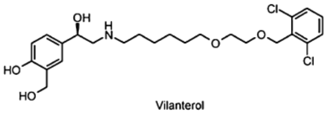
LABA



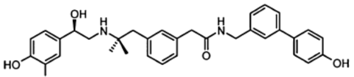
Indacaterol



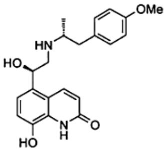
Olodaterol



Vilanterol



38 (PF-610355)

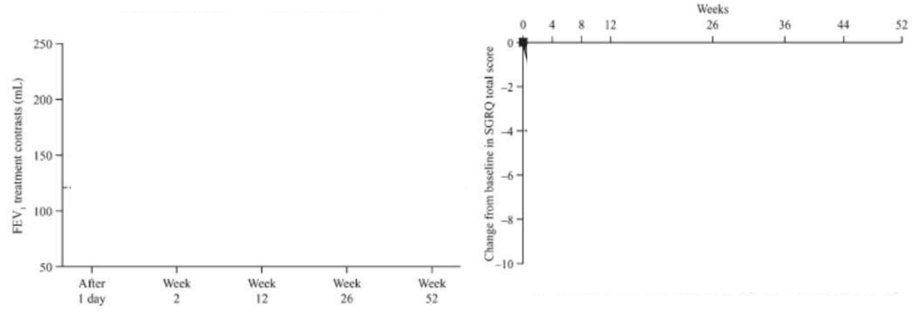


carmoterol$^{\$}$

Ultra LABA

Long term efficacy and safety of Indacaterol

N = 412 FEV$_1$ = 1.5 L DB,R, PC. 26 weeks Two doses versus placebo



No important adverse side effects

Decreased exacerbations by 14%

USA FDA approved 75 mcg

Chapman K et al CHEST 2011;140:68

Indacaterol versus Tiotropium

n = 1600

FEV1 = 1.5 l

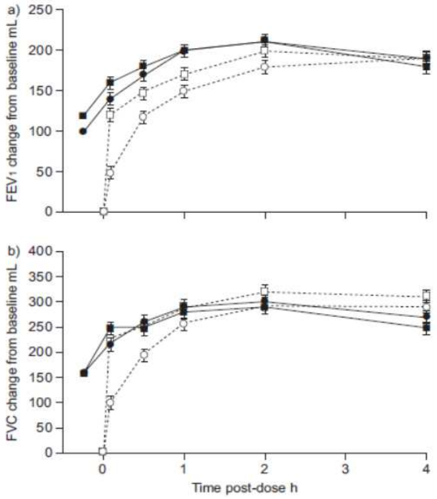
12 weeks

Indacaterol 150 mcg

Tiotropium 18 mcg

Outcomes

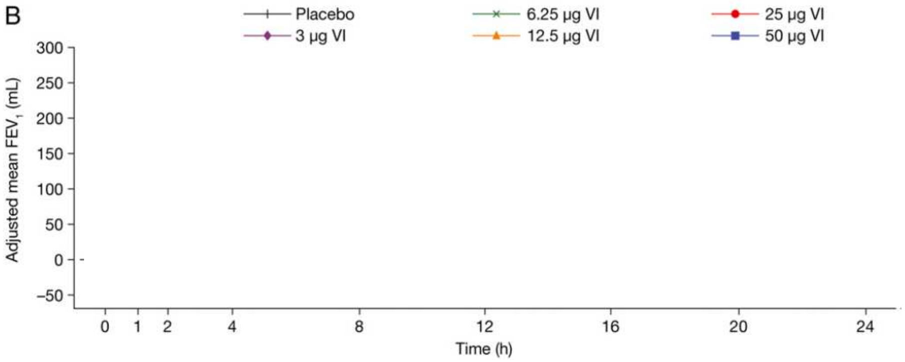
- **spirometry**
- **SGRQ**
- **TDI**



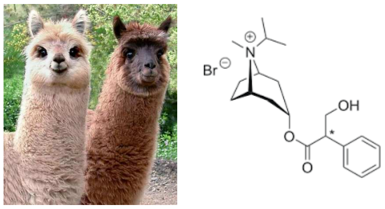
Buhl et al Eur Respir J 2011: 28:797

Efficacy and safety of Vilanterol

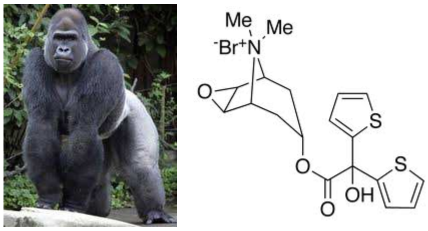
N = 602 FEV1 = 1.5 L DB,R, PC. 28 days 5 doses versus placebo



Hanania N et al CHEST 2012;142:199



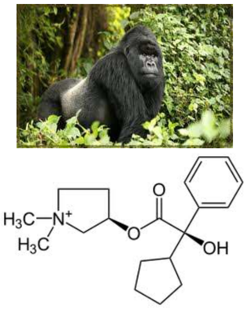
Ipratropium


Me
Me
⁻Br⁺N
O
S
O
OH
S
O

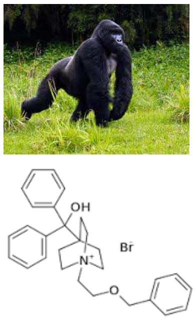
Tiotropium

LAMA

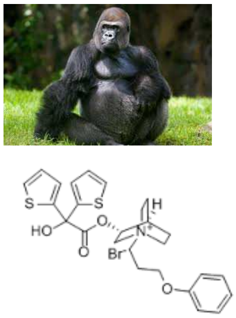
Glycopirronium


H₃C—N⁺
H₃C
O
O
OH

Umeclidinium

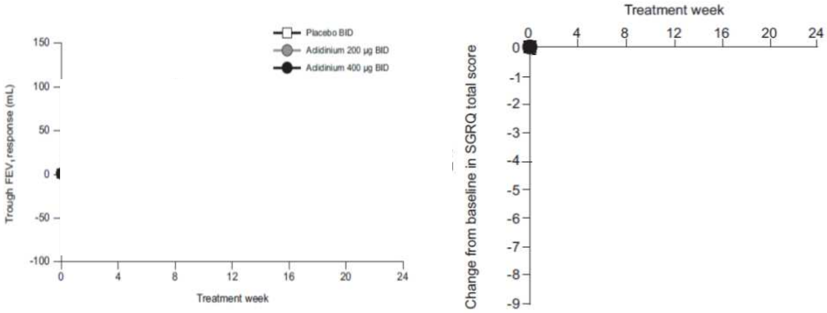


Aclidinium


S
S
HO
O
O
H
N⁺
Br⁻
O

Efficacy and safety of Aclidinium
The ATTAIN Study

N = 824 FEV1 = 1.5 L DB,R, PC. 24 weeks 2 doses versus placebo



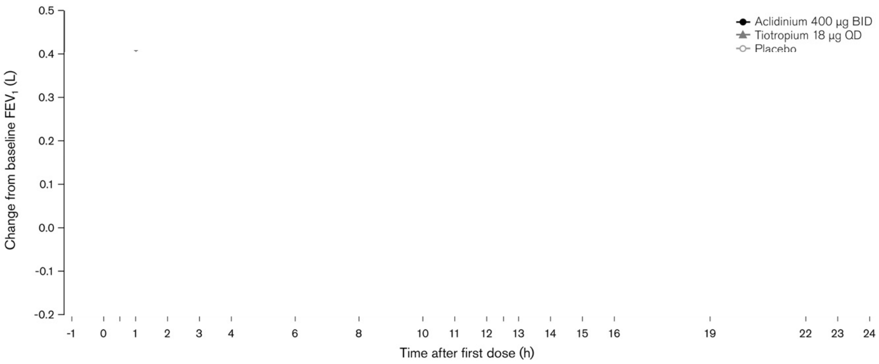
No difference in side effects versus placebo

TDI was also improved

Jones P et al Eur Respir J 2012 e published March 22

Aclidinium BID versus Tiotropium and Placebo

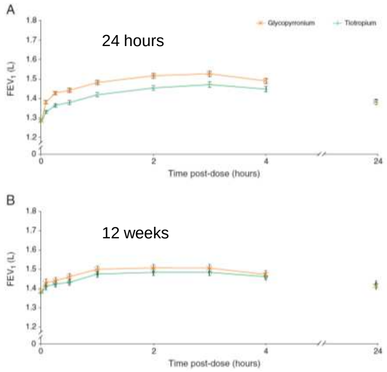
N = 30 FEV1 = 1.7 L R, PC. 15 days 2 medications versus placebo



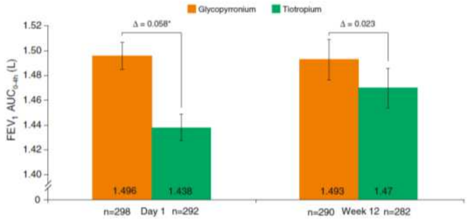
Furh R et al CHEST 2012;141:745

The GLOW study

N = 657   FEV$_1$ = 1.48 L DB,R, PC.   12 weeks   Tiotropium = 18 mcgr vs
Glycopirronium = 50 mcgr



AUC for FEV$_1$

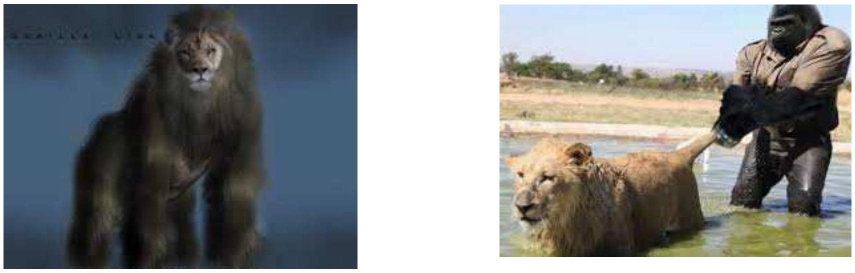


No difference in side effects

TDI was also improved

Chapman K et al et al BMC Pulm Med 2014;14:4

Where do we go from here?



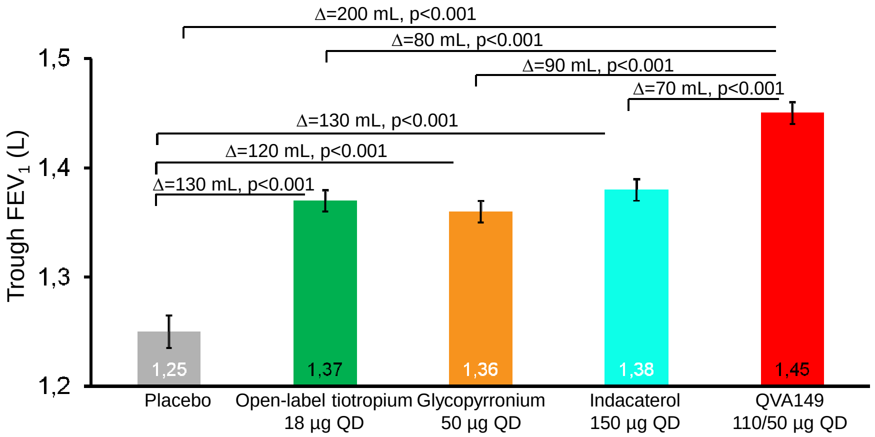
LABA + LAMA

Overview of inhaled LABA/LAMA

Drug combinations	Frequency	Company
Formoterol/ aclidinium	Twice daily	AZ
Formoterol/ glycopyrrolate	Twice daily	AZ
Olodaterol/ tiotropium	Once a day	BI
Umeclidinium/ vilanterol	Once a day	Theravance/GSK
Indacaterol/ glycopyrronium (QVA149)	Once a day	Novartis

QVA 149 versus 1 Bronchodilator (SHINE)

R, DB, PC, MC n = 2144 26 weeks FEV_1 = 1.5L Age = 64 years



SGRQ. QVA149 vs placebo = -3.64
QVA 149 vs Tiotropium = -2.34

Bateman et al. ERJ 2013;42:1484

Umeclidinium + Vilanterol versus Tiotropium and Vilanterol in COPD

R,DB, PC, MC

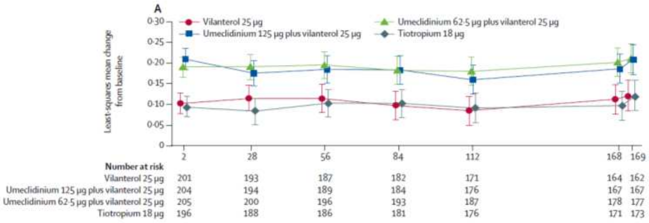
1141 patients

Age = 64 years

FEV_1 = 48 %

Duration 24 weeks

Change in FEV_1 at 24 weeks



Number at risk	2	28	56	84	112	168	169
Vilanterol 25 μg	201	193	187	182	171	164	162
Umeclidinium 125 μg plus vilanterol 25 μg	204	194	189	184	176	167	167
Umeclidinium 62·5 μg plus vilanterol 25 μg	205	200	196	193	187	178	177
Tiotropium 18 μg	196	188	186	181	176	171	173

TDI improved
No differences in TDI and exacerbation rate
Similar minimal side effects

Decramer et al Lancet RM 2014;6:472

Tiotropium + Olodaterol vs Tiotropium + Placebo in COPD

R,DB, PC, MC

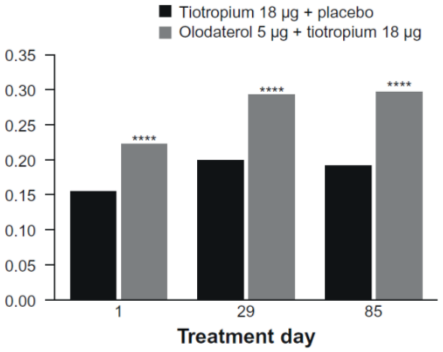
1134 patients

Age = 64 years

FEV_1 = 53 %

Duration 12 weeks

AUC for FEV_1 at 12 weeks



SGRQ improved
Difference from Tiotropium = - 1.83 units

ZuWallack R et al IJCOPD;2014;9:1133

Long Acting Bronchodilators
+
Inhaled Corticosteroid

Vilanterol + Fluticasone Furoate versus Fluticasone Propionate + Salmeterol in COPD

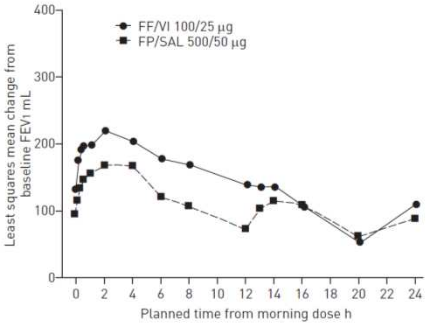
R,DB, PC, MC

528 patients

Age = 63 years

FEV$_1$ = 48 %

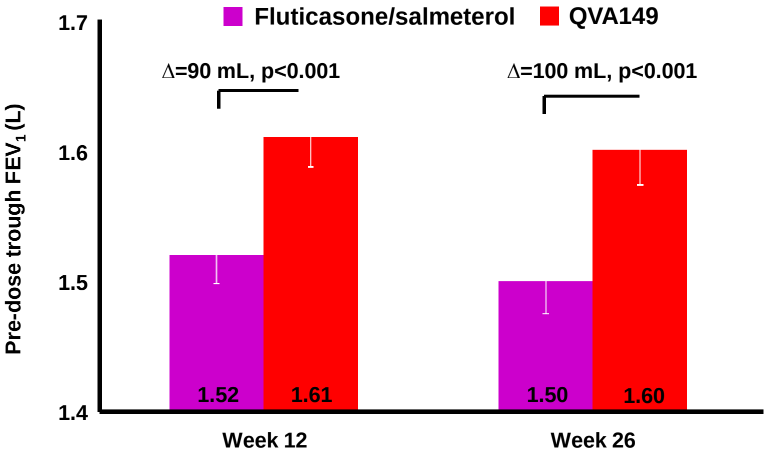
Duration 12 weeks



SGRQ difference = - 1.3 units
Pneumonia = similar (2)

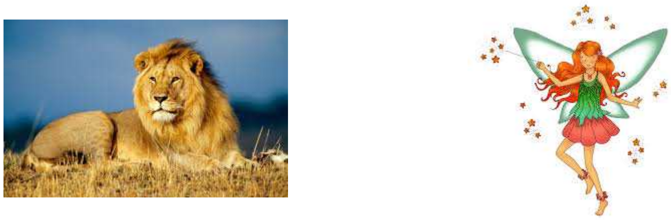
Agusti A et al ERJ;2014;43:763

QVA149 vs fluticasone/salmeterol at Week 12 and 26: IllUMINATE: n =523



Values are least squares means ± SE

Vogelmeier et al. ERS 2012



LABA + ICS

LABA + LAMA

Wisdom: Withdrawal of ICS and Exacerbations of COPD

DB, PG. 1year

1134 patients

On triple Rx then
ICS (F/S 500/50)
withdrawn over
12 weeks

Age = 63 years

FEV$_1$ = 34 %

SGRQ improved
Difference from Tiotropium = - 1.83 units

Magnussen H et al NEJM 2014;371:1285

Wisdom: Withdrawal of ICS and Exacerbations of COPD

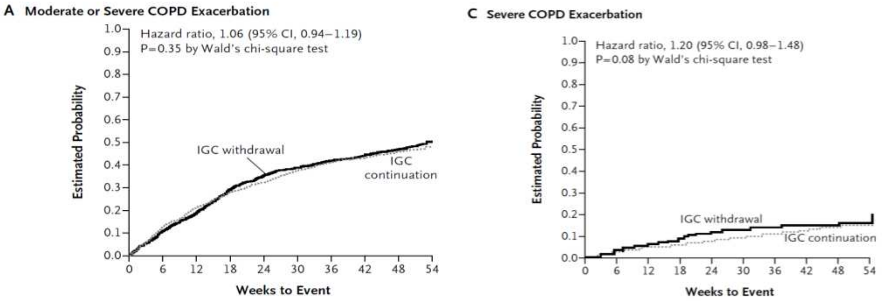
DB, PG. 1year

1134 patients

On triple Rx th
ICS (F/S 500/50)
withdrawn over
12 weeks

Age = 63 years

FEV1 = 34 %



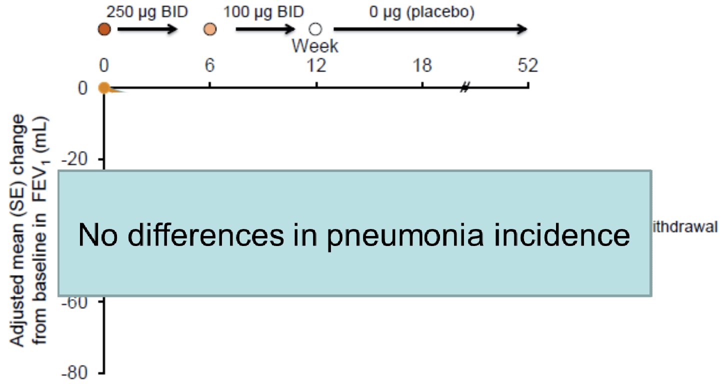
No. at Risk										
IGC continuation	1243	1059	927	827	763	694	646	615	581	14
IGC withdrawal	1242	1090	965	825	740	688	646	607	570	19

No. at Risk										
IGC continuation	1243	1180	1117	1066	1026	993	957	928	895	20
IGC withdrawal	1242	1189	1119	1044	986	941	918	889	863	25

SGRQ improved
Difference from Tiotropium = - 1.83 units

Magnussen H et al NEJM 2014;371:1285

WISDOM study: Mean FEV_1 change from baseline



No differences in pneumonia incidence

n					
ICS withdrawal	1223	1135	1114	1077	970
ICS	1218	1135	1092	1058	935

**p<0.01; ***p<0.0001 vs ICS; restricted maximum likelihood repeated measures model; baseline values 970 mL for ICS, 981 mL for ICS withdrawal
SE, standard error

Magnussen H et al NEJM 2014;371:1285

ORIGINAL ARTICLE

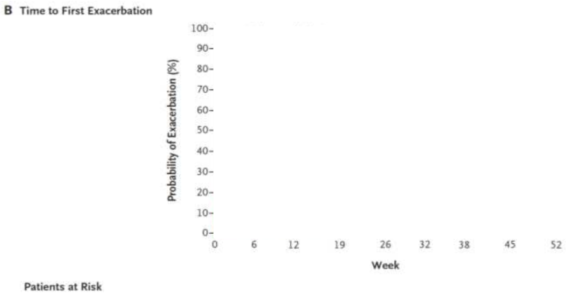
Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

DB, DD, R
Parallel groups
Multicenter
Non-inferiority

Hx of 1 AE the year before
3362 randomized

FEV1 = 1.2 L Age = 64 ys

Outcomes
- Exacerbations
- QoL
- FEV_1



Wedzicha W et al NEJM 2016;374:2222

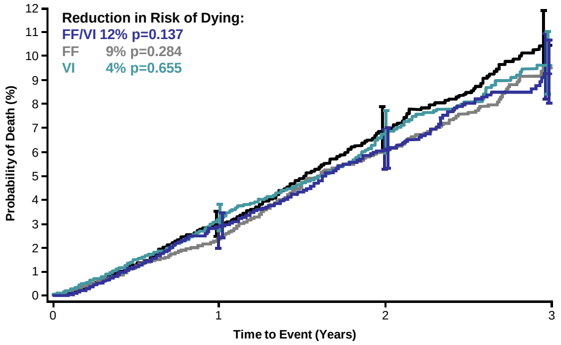
Fluticasone Furoate and Vilanterol and Survival and survival in COPD with heightened CV risk (SUMMIT): a DB randomized controlled trial

PC, R, DB, 4 arms
event driven trial
45 countries

16485 patients
FEV_1 = 1.7 L
Age = 64 years

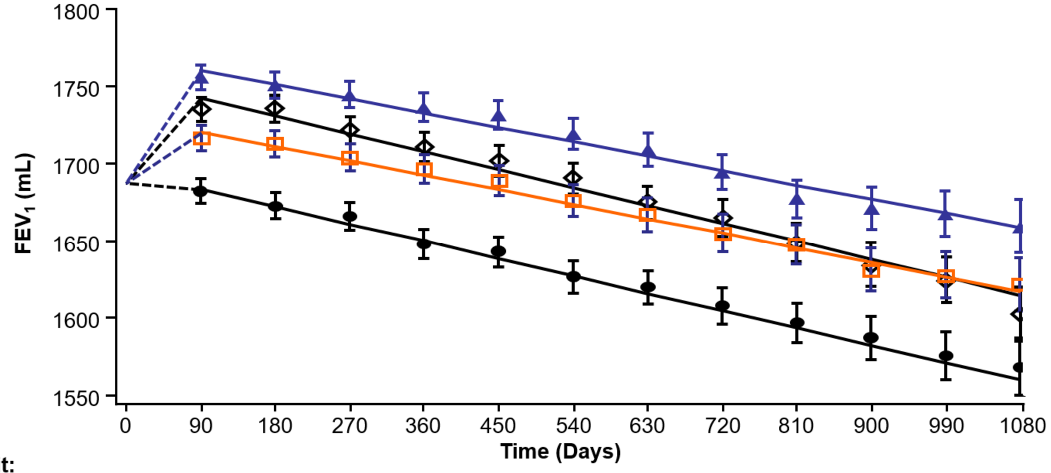
Mean treatment exposure 1.7 years

Outcomes = death



N alive:				
Placebo	4111	3465	1715	469
FF 100	4135	3499	1734	490
VI 25	4118	3466	1734	486
FF/VI 100/25	4121	3484	1718	485

Rate of decline in lung function: effect of treatment

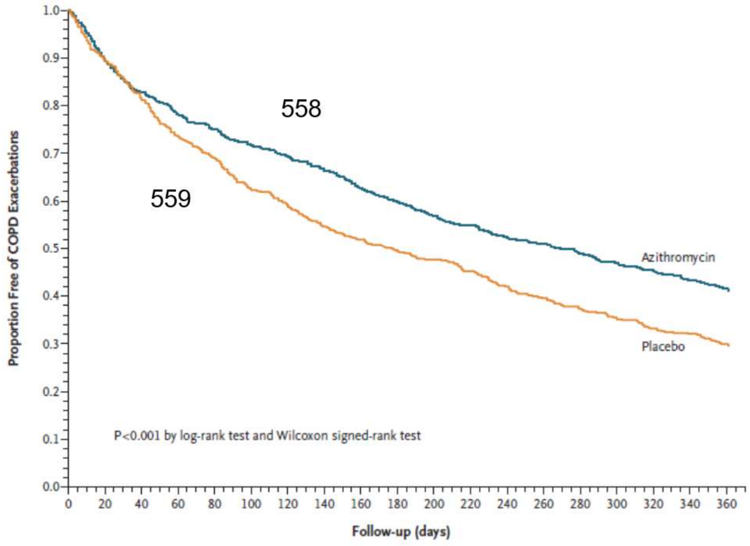


N at visit:

	0	90	180	270	360	450	540	630	720	810	900	990	1080
● Placebo	3800	3782	3563	3396	3279	2678	2197	1858	1498	1171	949	736	486
▲ FF/VI 100/25	3912	3883	3731	3610	3505	2864	2391	1997	1633	1290	1035	827	545
□ FF 100	3879	3858	3688	3580	3452	2777	2311	1936	1569	1246	1001	792	528
◇ VI 25	3866	3830	3658	3554	3438	2813	2347	1971	1612	1300	1043	831	542

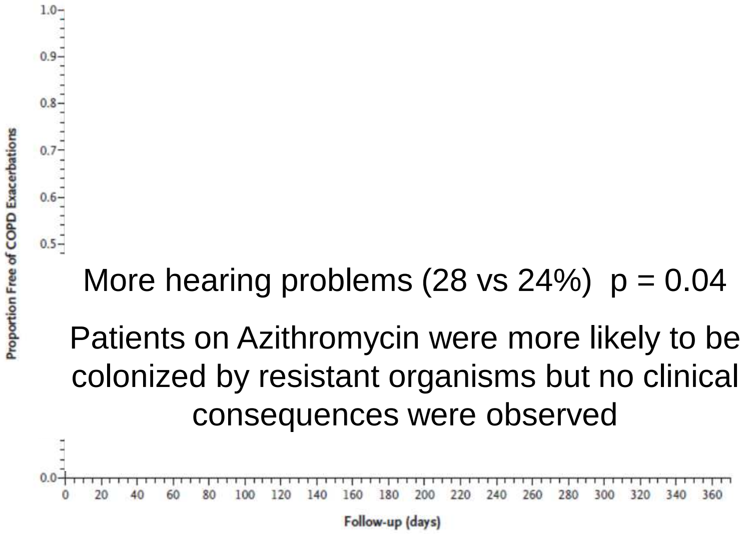
Symbols represent adjusted means from the RM model and lines come from model for slopes

Azithromycin for prevention of exacerbations of COPD



Albert R et al NEJM 2011;365:689

Azithromycin for prevention of exacerbations of COPD



More hearing problems (28 vs 24%) p = 0.04

Patients on Azithromycin were more likely to be colonized by resistant organisms but no clinical consequences were observed

Albert R et al NEJM 2011;365:689

How to approach?

ICS + LABA

LABA + LAMA

PDEI 4

LABA

LAMA

SABA

SAMA

Diagnosis → **Assessment of airflow limitation**

$FEV_1/FVC<0.7$

Grade	FEV_1 (% pred.)
1	≥80
2	50-79
3	30-49
4	<30

Diagnosis → **Assessment of airflow limitation** → **Assessment of symptoms/risk of exacerbations**

$FEV_1/FVC<0.7$

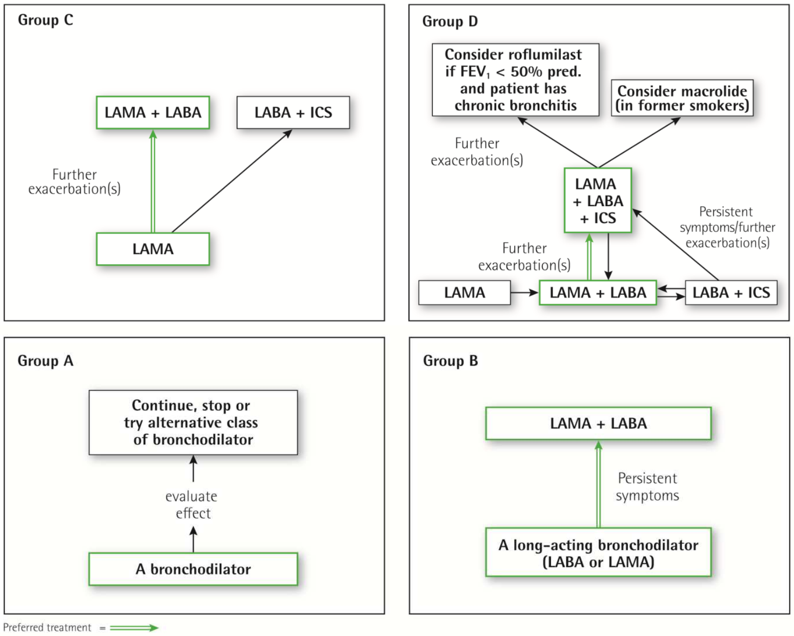
Grade	FEV_1 (% pred.)
1	≥80
2	50-79
3	30-49
4	<30

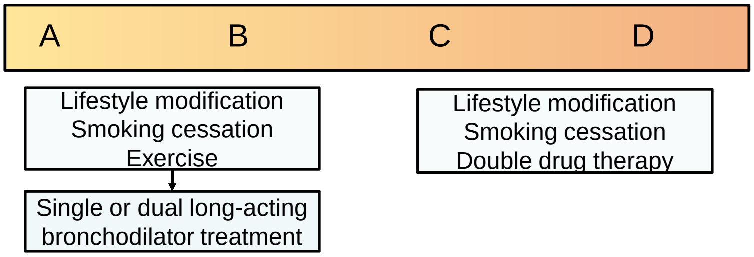
Exacerbation history

2 or more or 1 or more leading to hospital admission	**C**	**D**
0 or 1 (not leading to hospital admission)	**A**	**B**
	mMRC 0-1 CAT < 10 CCQ < 1	mMRC 2+ CAT 10+ CCQ 1+

Rationalizing Pharmacotherapy

Asthma & COPD Medications


Group C
LAMA + LABA
LABA + ICS
Further exacerbation(s)
LAMA
Group D
Consider roflumilast if FEV₁ < 50% pred. and patient has chronic bronchitis
Consider macrolide (in former smokers)
Further exacerbation(s)
LAMA + LABA + ICS
Persistent symptoms/further exacerbation(s)
Further exacerbation(s)
LAMA
LAMA + LABA
LABA + ICS
Group A
Continue, stop or try alternative class of bronchodilator
evaluate effect
A bronchodilator
Group B
LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)
Preferred treatment =



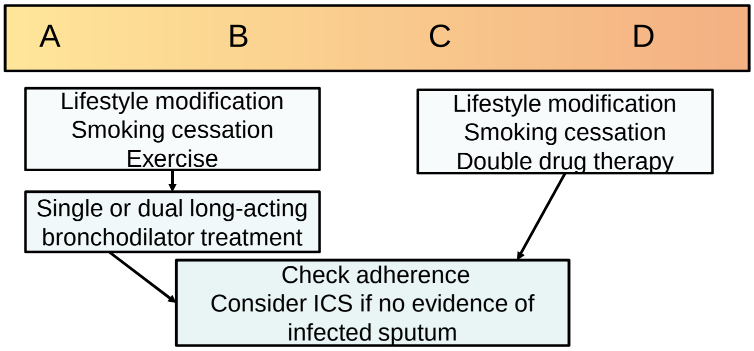
A B C D

Lifestyle modification
Smoking cessation
Exercise

Single or dual long-acting bronchodilator treatment

Lifestyle modification
Smoking cessation
Double drug therapy

GOLD. Modified by Celli



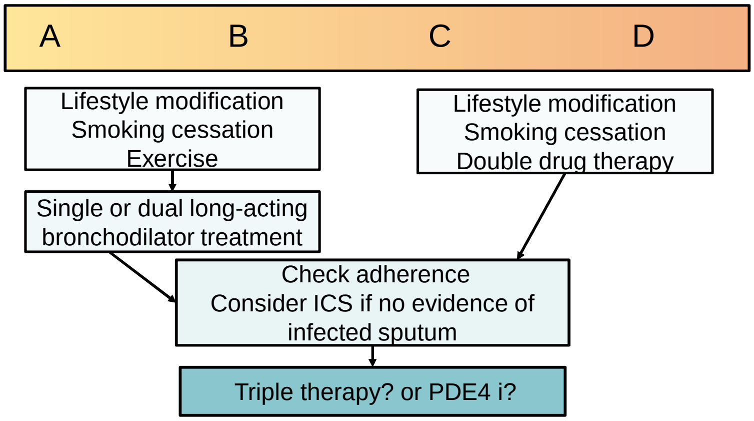
Lifestyle modification
Smoking cessation
Exercise

Single or dual long-acting bronchodilator treatment

Lifestyle modification
Smoking cessation
Double drug therapy

Check adherence
Consider ICS if no evidence of infected sputum

GOLD. Modified by Celli



Lifestyle modification
Smoking cessation
Exercise

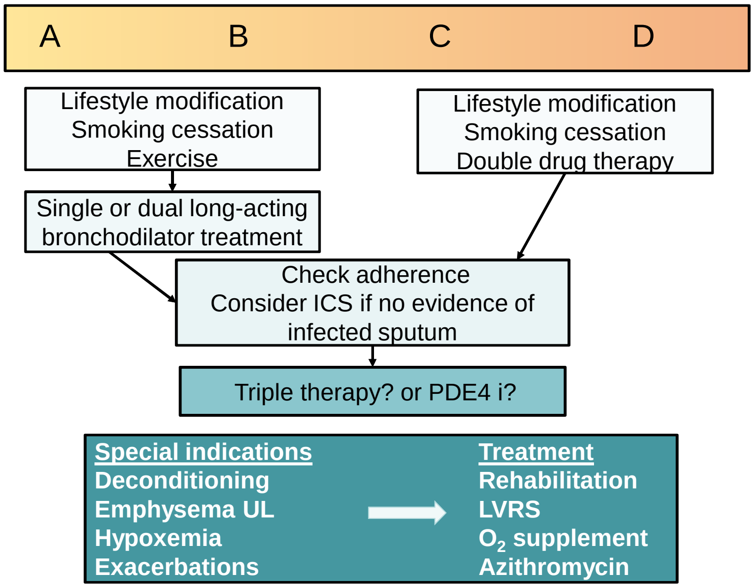
Single or dual long-acting bronchodilator treatment

Lifestyle modification
Smoking cessation
Double drug therapy

Check adherence
Consider ICS if no evidence of infected sputum

Triple therapy? or PDE4 i?

GOLD. Modified by Celli



A B C D

Lifestyle modification
Smoking cessation
Exercise

Single or dual long-acting
bronchodilator treatment

Lifestyle modification
Smoking cessation
Double drug therapy

Check adherence
Consider ICS if no evidence of
infected sputum

Triple therapy? or PDE4 i?

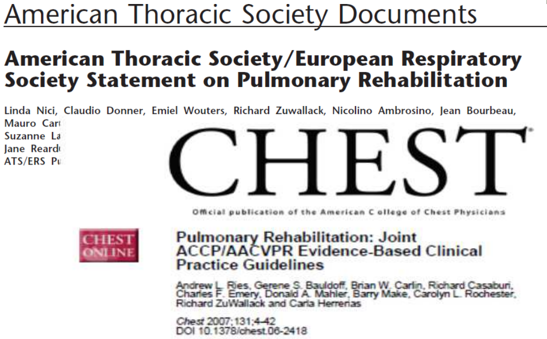
Special indications		**Treatment**
Deconditioning	→	**Rehabilitation**
Emphysema UL		**LVRS**
Hypoxemia		**O_2 supplement**
Exacerbations		**Azithromycin**

GOLD. Modified by Celli

Rehabilitation

Unbeatable

Evidence A



American Thoracic Society Documents

American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation

Linda Nici, Claudio Donner, Emiel Wouters, Richard Zuwallack, Nicolino Ambrosino, Jean Bourbeau,
Mauro Car
Suzanne La
Jane Reard
ATS/ERS Pu

CHEST

Official publication of the American College of Chest Physicians

CHEST ONLINE

Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines

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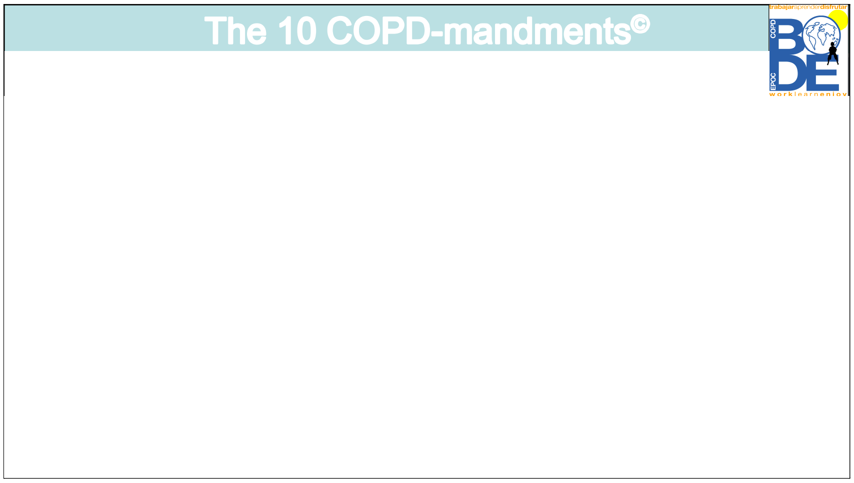
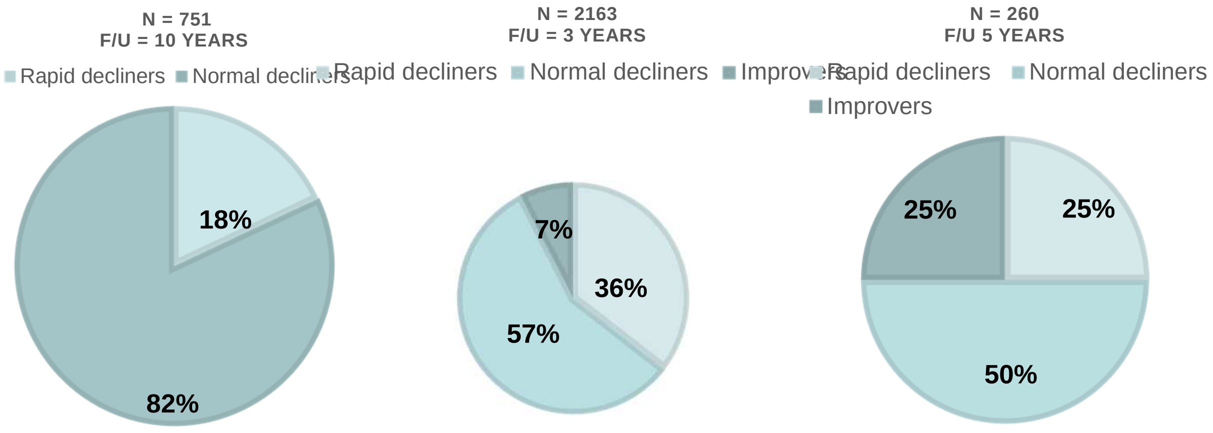
Chest 2007;131;4-42
DOI 10.1378/chest.06-2418



The 10 COPD-mandments©

Marin J et al Arch Bronconeumol 2016;52:179

Rate of FEV_1 decline in 3 observational studies of patients with COPD



Casanova C et al AJRCCM 2011;184:315

Vestbo J et al N Engl J Med 2011; 365:1184

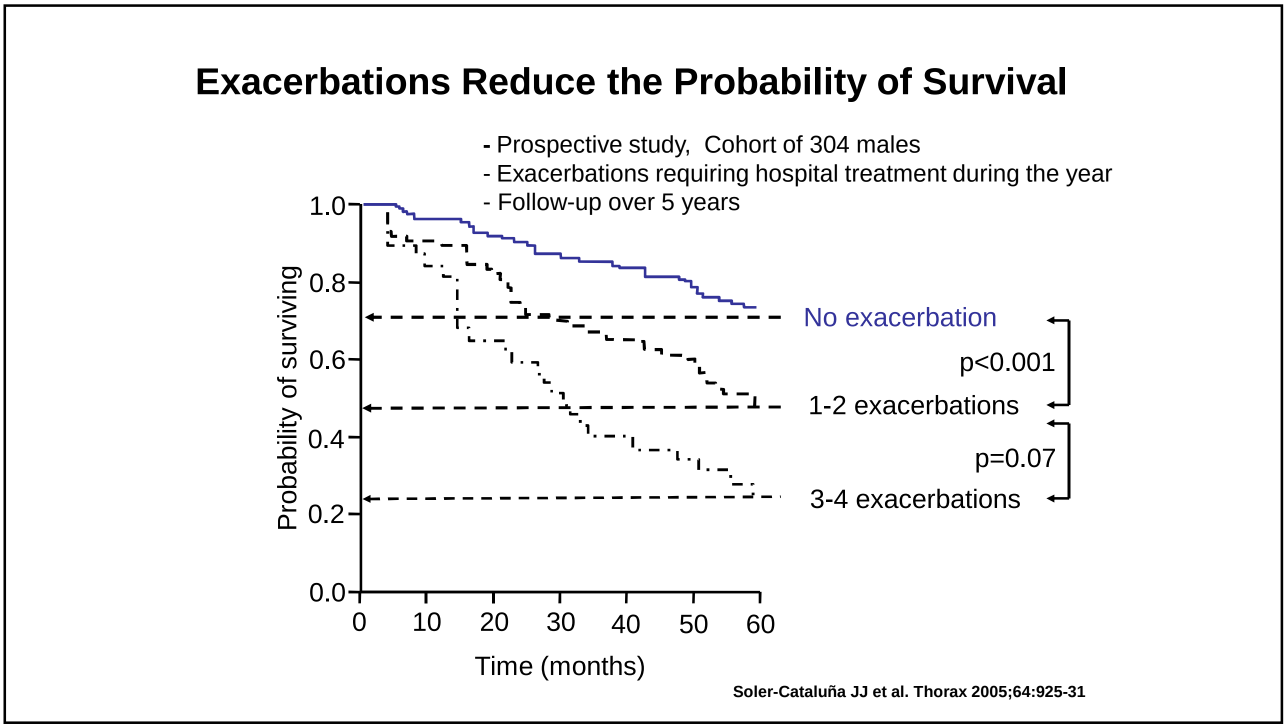
Nishimura M et al AJRCCM 2012;185:44

Exacerbations

What do these patients have in common?

[redacted] [redacted]

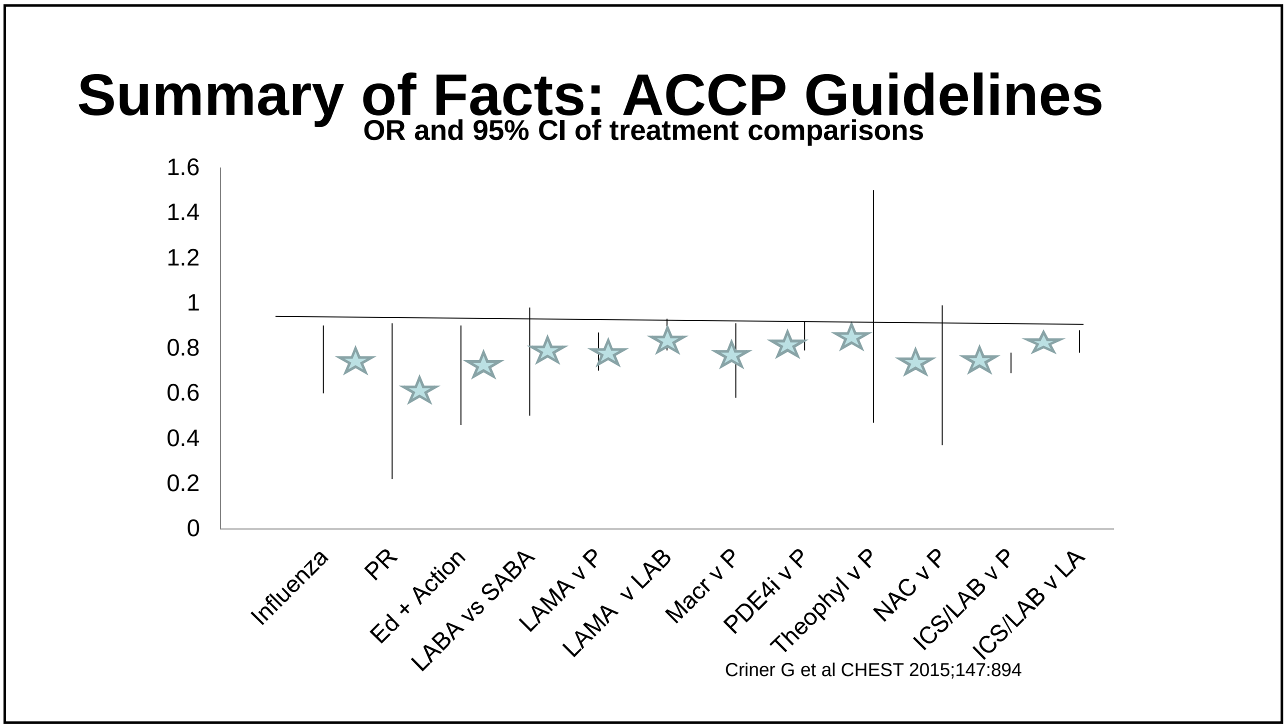
COPD & Exacerbation



Exacerbations Reduce the Probability of Survival

- Prospective study, Cohort of 304 males
- Exacerbations requiring hospital treatment during the year
- Follow-up over 5 years

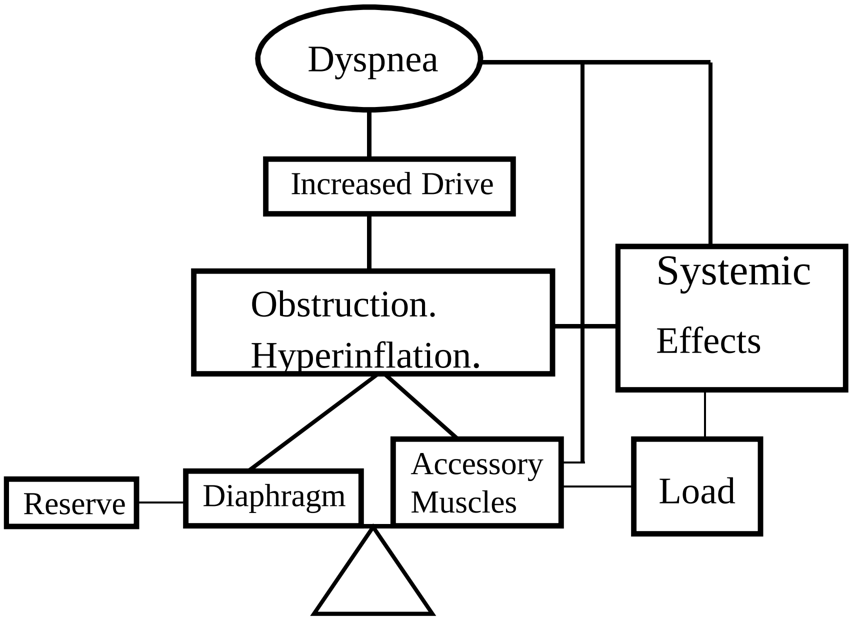
Soler-Cataluña JJ et al. Thorax 2005;64:925-31



Summary of Facts: ACCP Guidelines

OR and 95% CI of treatment comparisons

Criner G et al CHEST 2015;147:894



Dyspnea

Increased Drive

Obstruction.
Hyperinflation.

Systemic
Effects

Reserve

Diaphragm

Accessory
Muscles

Load

Rest

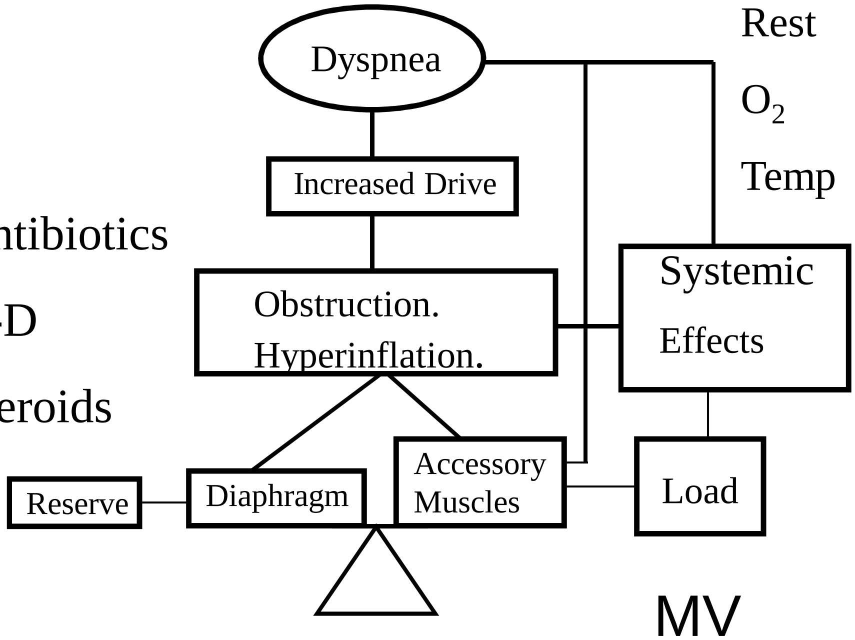
O_2

Temp

Antibiotics

B-D

Steroids



Dyspnea

Increased Drive

Obstruction.
Hyperinflation.

Systemic
Effects

Reserve

Diaphragm

Accessory
Muscles

Load

MV

Controlled trial of antibiotics in Ventilated Exacerbation of COPD

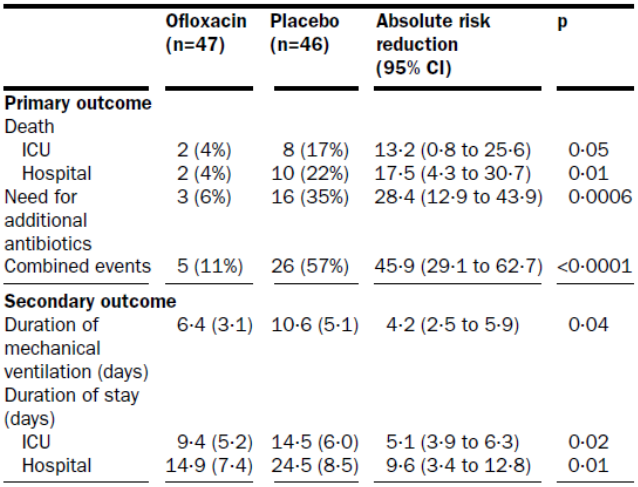
DB, PC, R

n = 93 on MV

Oxiflacina
versus
Placebo

10 days

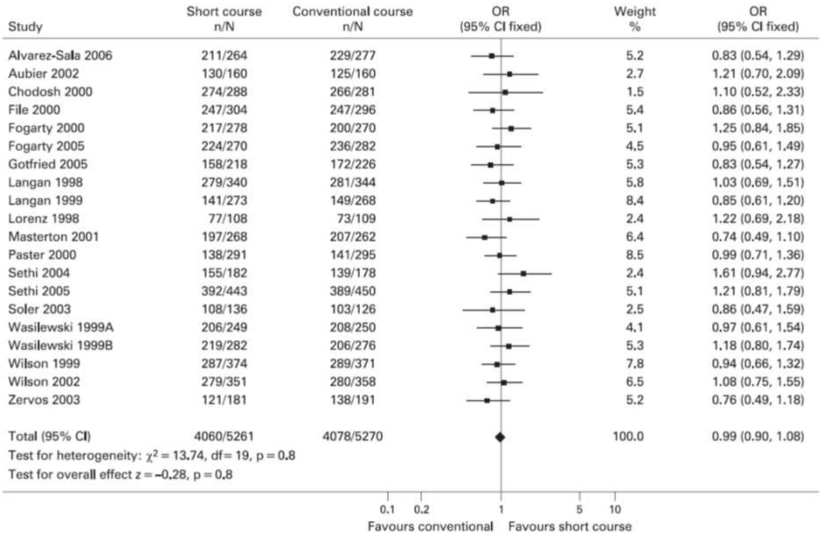
Outcomes:
- Death
- Need for ab
- MV duration



	Ofloxacin (n=47)	**Placebo (n=46)**	**Absolute risk reduction (95% CI)**	**p**
Primary outcome				
Death				
ICU	2 (4%)	8 (17%)	13·2 (0·8 to 25·6)	0·05
Hospital	2 (4%)	10 (22%)	17·5 (4·3 to 30·7)	0·01
Need for additional antibiotics	3 (6%)	16 (35%)	28·4 (12·9 to 43·9)	0·0006
Combined events	5 (11%)	26 (57%)	45·9 (29·1 to 62·7)	<0·0001
Secondary outcome				
Duration of mechanical ventilation (days)	6·4 (3·1)	10·6 (5·1)	4·2 (2·5 to 5·9)	0·04
Duration of stay (days)				
ICU	9·4 (5·2)	14·5 (6·0)	5·1 (3·9 to 6·3)	0·02
Hospital	14·9 (7·4)	24·5 (8·5)	9·6 (3·4 to 12·8)	0·01

Nouira S et al Lancet 2001;358:2020

Treatment of Short versus Long term antibiotics



Study	Short course n/N	Conventional course n/N	Weight %	OR (95% CI fixed)
Alvarez-Sala 2006	211/264	229/277	5.2	0.83 (0.54, 1.29)
Aubier 2002	130/160	125/160	2.7	1.21 (0.70, 2.09)
Chodosh 2000	274/288	266/281	1.5	1.10 (0.52, 2.33)
File 2000	247/304	247/296	5.4	0.86 (0.56, 1.31)
Fogarty 2000	217/278	200/270	5.1	1.25 (0.84, 1.85)
Fogarty 2005	224/270	236/282	4.5	0.95 (0.61, 1.49)
Gotfried 2005	158/218	172/226	5.3	0.83 (0.54, 1.27)
Langan 1998	279/340	281/344	5.8	1.03 (0.69, 1.51)
Langan 1999	141/273	149/268	8.4	0.85 (0.61, 1.20)
Lorenz 1998	77/108	73/109	2.4	1.22 (0.69, 2.18)
Masterton 2001	197/268	207/262	6.4	0.74 (0.49, 1.10)
Paster 2000	138/291	141/295	8.5	0.99 (0.71, 1.36)
Sethi 2004	155/182	139/178	2.4	1.61 (0.94, 2.77)
Sethi 2005	392/443	389/450	5.1	1.21 (0.81, 1.79)
Soler 2003	108/136	103/126	2.5	0.86 (0.47, 1.59)
Wasilewski 1999A	206/249	208/250	4.1	0.97 (0.61, 1.54)
Wasilewski 1999B	219/282	206/276	5.3	1.18 (0.80, 1.74)
Wilson 1999	287/374	289/371	7.8	0.94 (0.66, 1.32)
Wilson 2002	279/351	280/358	6.5	1.08 (0.75, 1.55)
Zervos 2003	121/181	138/191	5.2	0.76 (0.49, 1.18)
Total (95% CI)	4060/5261	4078/5270	100.0	0.99 (0.90, 1.08)

Test for heterogeneity: $\chi^2 = 13.74$, df= 19, p = 0.8

Test for overall effect z = –0.28, p = 0.8

Moussai et al Thorax 2008;63:415

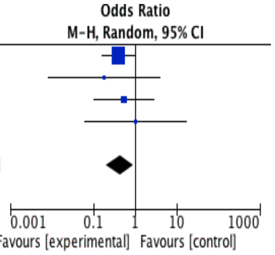
Corticosteroids

For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we suggest that systemic corticosteroids be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30-days following the initial exacerbation (Grade 2B).

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Aaron 2003	8	72	17	71	66.8%	0.40 [0.16, 0.99]
Agarwall 2011	0	50	2	47	6.0%	0.18 [0.01, 3.85]
Niewoehner 1999	2	80	5	111	20.1%	0.54 [0.10, 2.88]
Stalberg 2009	1	54	1	55	7.1%	1.02 [0.06, 16.71]
Total (95% CI)		**256**		**284**	**100.0%**	**0.43 [0.20, 0.91]**
Total events	11		25			

Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.78$, df = 3 (P = 0.85); $I^2 = 0\%$

Test for overall effect: Z = 2.20 (P = 0.03)



Criner G et al CHEST 2015;147:894

Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Review)

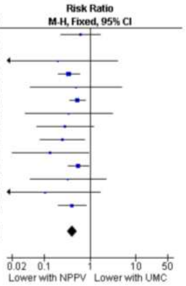
Intubation

Figure 4. Forest plot of comparison: 1 NPPV +Usual Medical Care vs Usual Medical Care - Overall, outcome: 1.3 Intubation.

Study or Subgroup	NPPV Events	NPPV Total	UMC Events	UMC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Avdeev 1998	5	29	8	29	5.2%	0.63 [0.23, 1.68]
Barbe 1996	0	10	0	10		Not estimable
Bott 1993	0	30	2	30	1.6%	0.20 [0.01, 4.00]
Brochard 1995	11	43	31	42	20.3%	0.35 [0.20, 0.60]
Celikel 1998	1	15	2	15	1.3%	0.50 [0.05, 4.94]
Conti 2002	12	23	26	26	16.2%	0.53 [0.36, 0.78]
del Castillo 2003	1	20	3	21	1.9%	0.35 [0.04, 3.09]
Dikensoy 2002	2	17	7	17	4.5%	0.29 [0.07, 1.18]
Khilnani 2002	3	20	12	20	7.8%	0.25 [0.08, 0.75]
Kramer 1995	1	11	8	12	5.0%	0.14 [0.02, 0.92]
Plant 2000	18	118	32	118	20.7%	0.56 [0.34, 0.94]
Servillo 1994	1	5	3	5	1.9%	0.33 [0.05, 2.21]
Thys 2002	0	7	3	5	2.6%	0.11 [0.01, 1.71]
Zhou 2001	7	30	17	30	11.0%	0.41 [0.20, 0.85]
Total (95% CI)		**378**		**380**	**100.0%**	**0.42 [0.33, 0.53]**
Total events	62		154			

Heterogeneity: $\text{Chi}^2 = 7.58$, df = 12 (P = 0.82); $I^2 = 0\%$

Test for overall effect: Z = 7.20 (P < 0.00001)



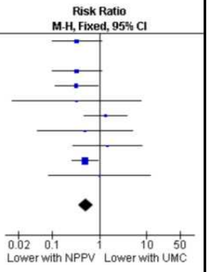
Mortality

Figure 3. Forest plot of comparison: 1 NPPV +Usual Medical Care vs Usual Medical Care - Overal outcome: 1.2 Mortality.

Study or Subgroup	NPPV Events	NPPV Total	UMC Events	UMC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Avdeev 1998	3	29	9	29	13.8%	0.33 [0.10, 1.11]
Barbe 1996	0	10	0	10		Not estimable
Bott 1993	3	30	9	30	13.8%	0.33 [0.10, 1.11]
Brochard 1995	4	43	12	42	18.6%	0.33 [0.11, 0.93]
Celikel 1998	0	15	1	15	2.3%	0.33 [0.01, 7.58]
Conti 2002	6	23	5	26	7.2%	1.36 [0.48, 3.86]
Dikensoy 2002	1	17	2	17	3.1%	0.50 [0.05, 5.01]
Khilnani 2002	3	20	2	20	3.1%	1.50 [0.28, 8.04]
Plant 2000	12	118	24	118	36.7%	0.50 [0.26, 0.95]
Servillo 1994	1	5	1	5	1.5%	1.00 [0.08, 11.93]
Total (95% CI)		**310**		**312**	**100.0%**	**0.52 [0.35, 0.76]**
Total events	33		65			

Heterogeneity: $\text{Chi}^2 = 6.94$, df = 8 (P = 0.54); $I^2 = 0\%$

Test for overall effect: Z = 3.37 (P = 0.0008)



Ram SJ et al Cochrane Review 2009

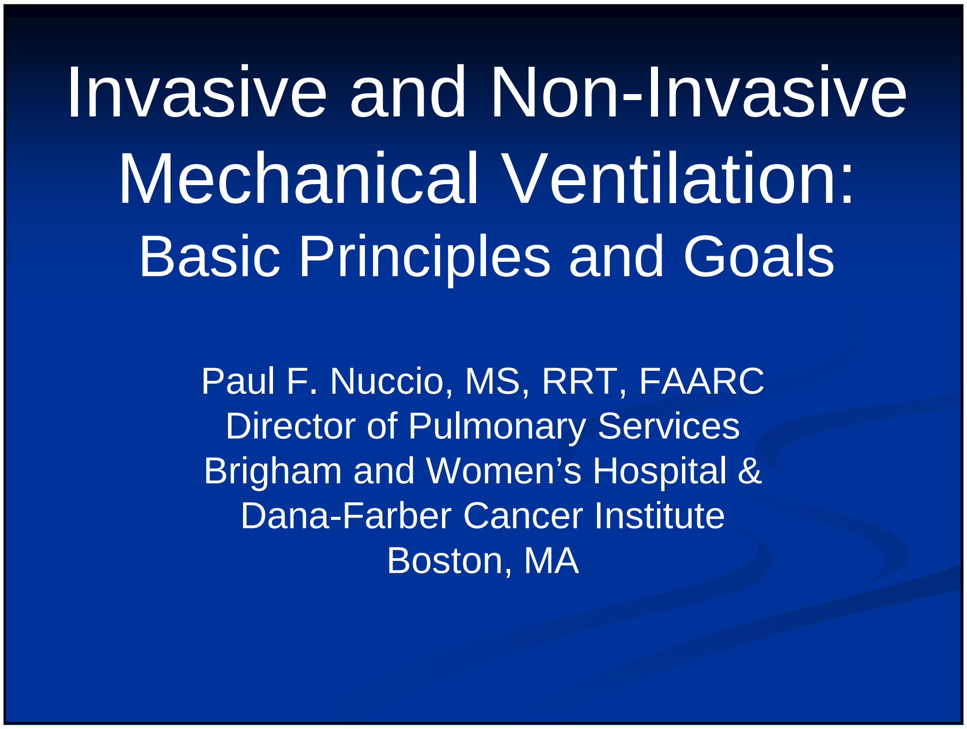
Conclusions

- We need to promote healthy lifestyles and battle against smoking and pollution
- There is a need to improve diagnosis of COPD
- Pharmacotherapy is effective if well used
- Rehabilitation is a “must consider”
- Exacerbations should be prevented and treated
- Onwards, the future is ours to build

Thank You

References

1. Vogelmeier C et al. Global strategy for the diagnosis and management and prevention of COPD. American J Respir and Crit Care Med. 2017; 195:557
2. Criner G. et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Guidelines. CHEST 2015;147:894
3. Celli B et al. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. Eur Respir Rev. 2015;24:159



Invasive and Non-Invasive Mechanical Ventilation:

Basic Principles and Goals

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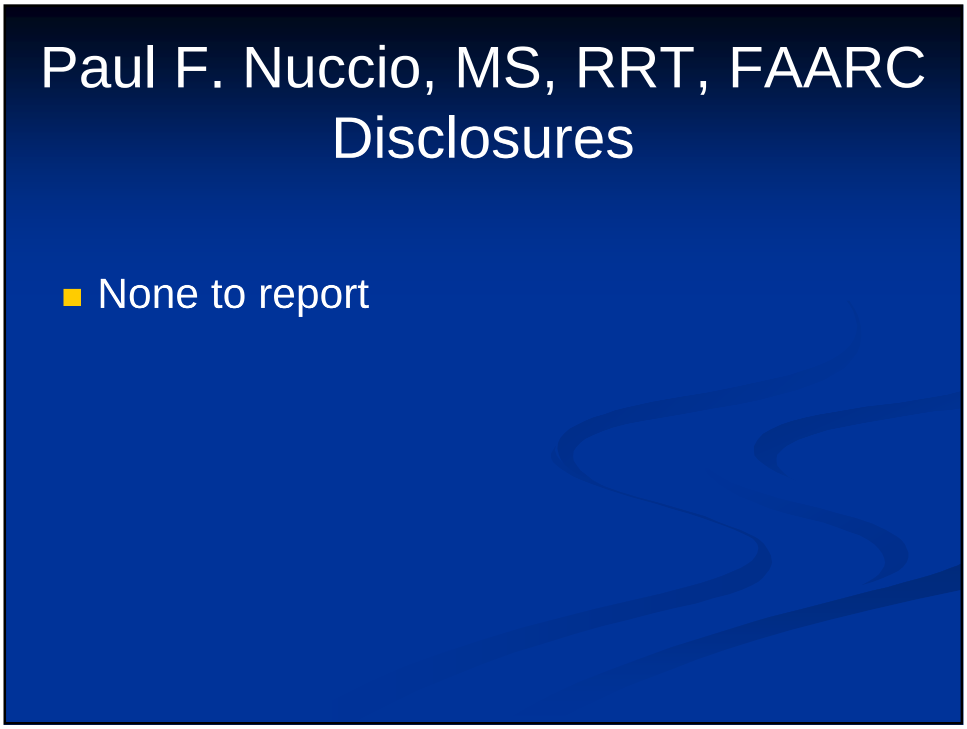
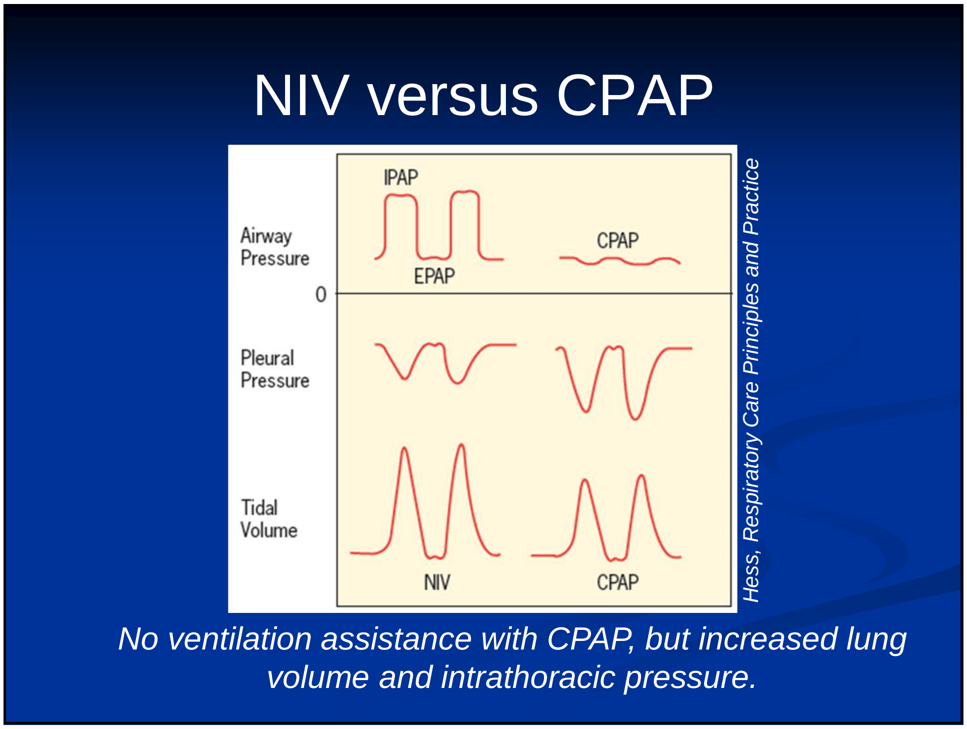


Paul F. Nuccio, MS, RRT, FAARC Disclosures

- None to report

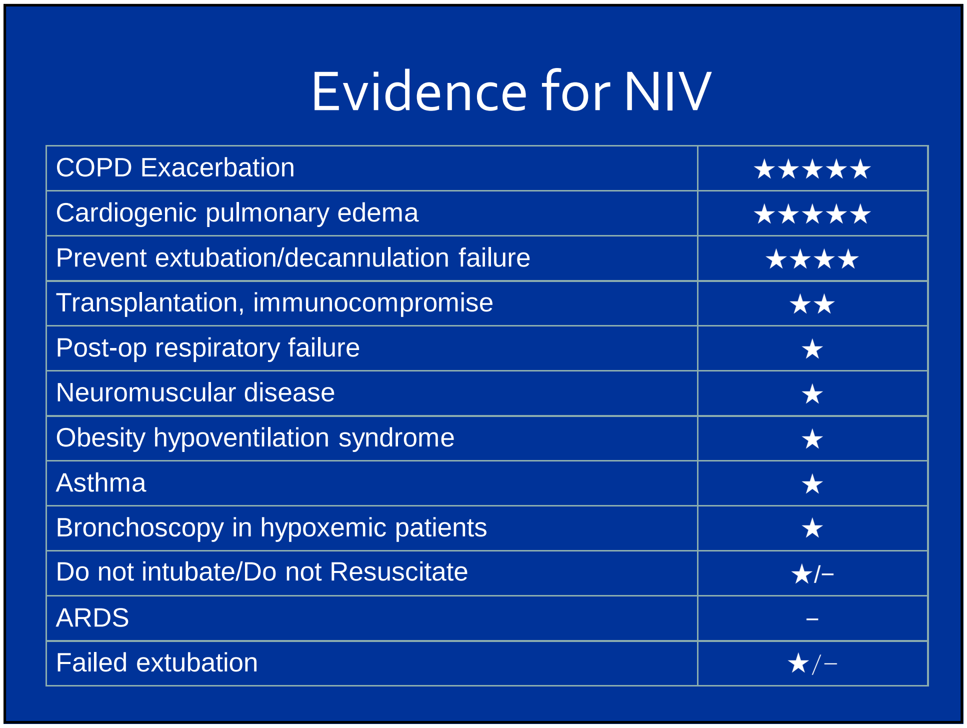


NIV versus CPAP

Airway Pressure
Pleural Pressure
Tidal Volume
0
IPAP
EPAP
CPAP
NIV
CPAP

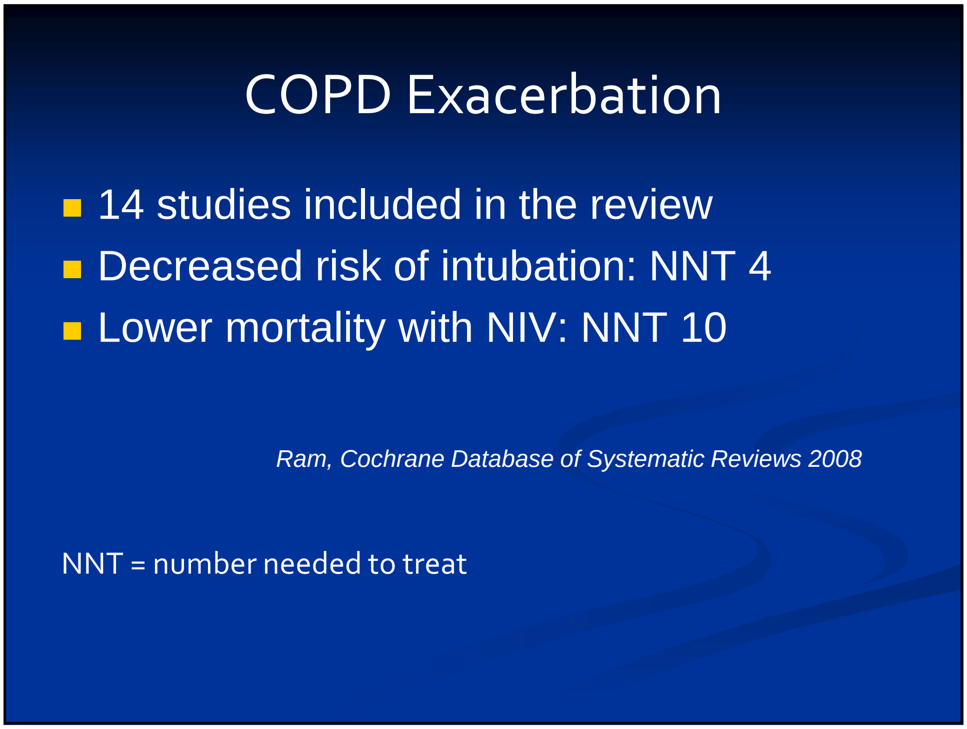
Hess, Respiratory Care Principles and Practice

No ventilation assistance with CPAP, but increased lung volume and intrathoracic pressure.



Evidence for NIV

COPD Exacerbation	★★★★★
Cardiogenic pulmonary edema	★★★★★
Prevent extubation/decannulation failure	★★★★
Transplantation, immunocompromise	★★
Post-op respiratory failure	★
Neuromuscular disease	★
Obesity hypoventilation syndrome	★
Asthma	★
Bronchoscopy in hypoxemic patients	★
Do not intubate/Do not Resuscitate	★/−
ARDS	−
Failed extubation	★/−

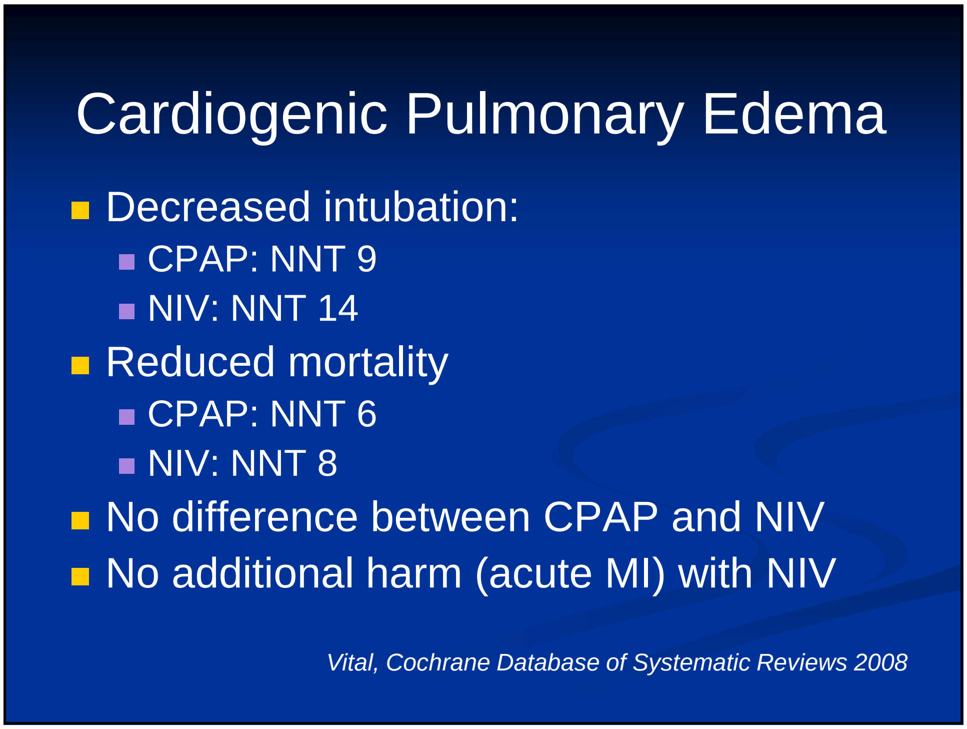


COPD Exacerbation

- 14 studies included in the review
- Decreased risk of intubation: NNT 4
- Lower mortality with NIV: NNT 10

Ram, Cochrane Database of Systematic Reviews 2008

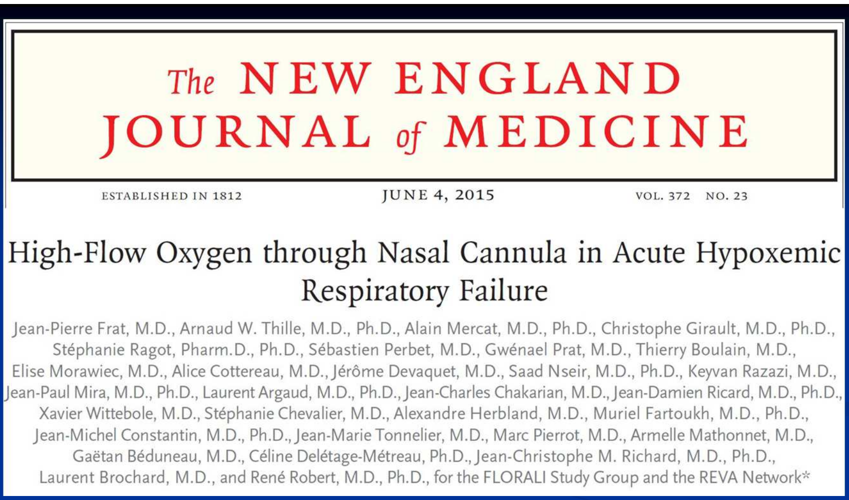
NNT = number needed to treat



Cardiogenic Pulmonary Edema

- Decreased intubation:
  - CPAP: NNT 9
  - NIV: NNT 14
- Reduced mortality
  - CPAP: NNT 6
  - NIV: NNT 8
- No difference between CPAP and NIV
- No additional harm (acute MI) with NIV

Vital, Cochrane Database of Systematic Reviews 2008



The NEW ENGLAND JOURNAL of MEDICINE

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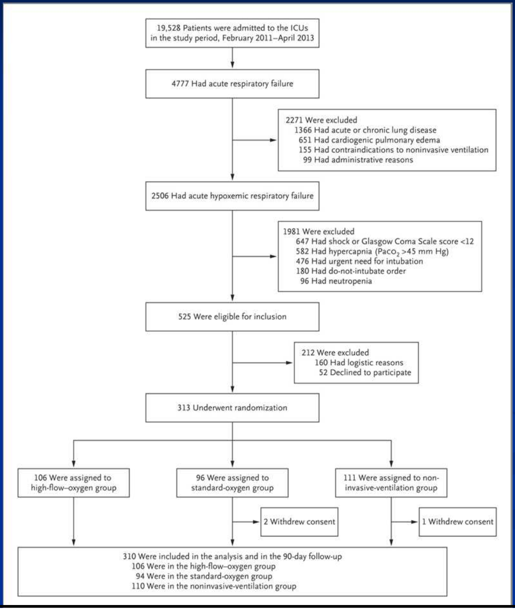
High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

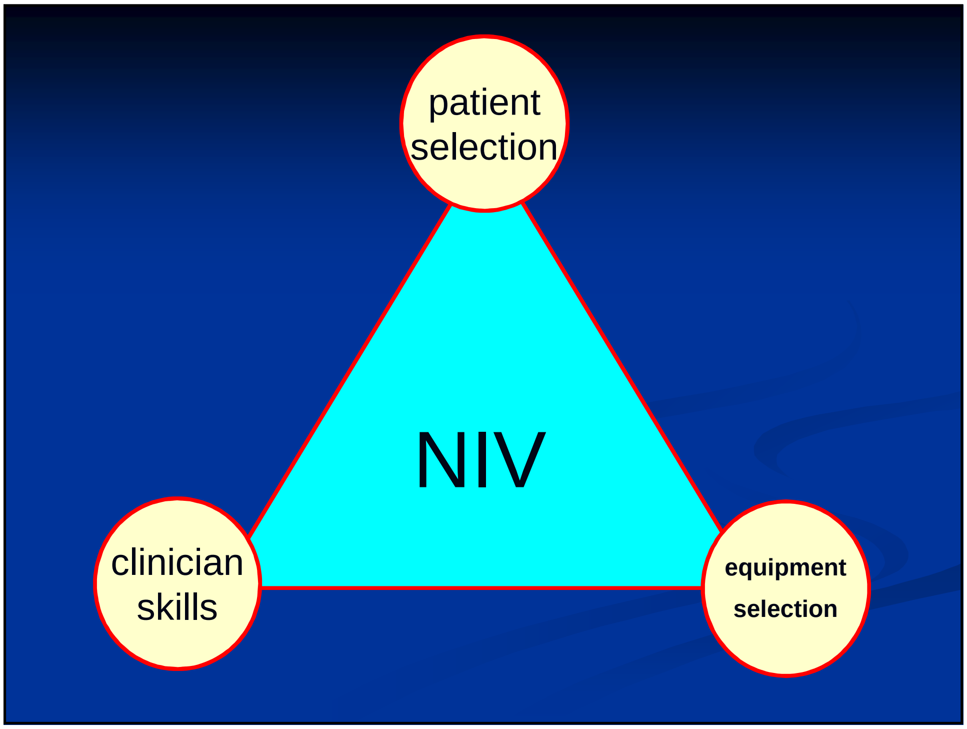
Jean-Pierre Frat, M.D., Arnaud W. Thille, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Christophe Girault, M.D., Ph.D., Stéphanie Ragot, Pharm.D., Ph.D., Sébastien Perbet, M.D., Gwénael Prat, M.D., Thierry Boulain, M.D., Elise Morawiec, M.D., Alice Cottereau, M.D., Jérôme Devaquet, M.D., Saad Nseir, M.D., Ph.D., Keyvan Razazi, M.D., Jean-Paul Mira, M.D., Ph.D., Laurent Argaud, M.D., Ph.D., Jean-Charles Chakarian, M.D., Jean-Damien Ricard, M.D., Ph.D., Xavier Wittebole, M.D., Stéphanie Chevalier, M.D., Alexandre Herbland, M.D., Muriel Fartoukh, M.D., Ph.D., Jean-Michel Constantin, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Marc Pierrot, M.D., Armelle Mathonnet, M.D., Gaëtan Béduneau, M.D., Céline Delétage-Métreau, Ph.D., Jean-Christophe M. Richard, M.D., Ph.D., Laurent Brochard, M.D., and René Robert, M.D., Ph.D., for the FLORALI Study Group and the REVA Network*

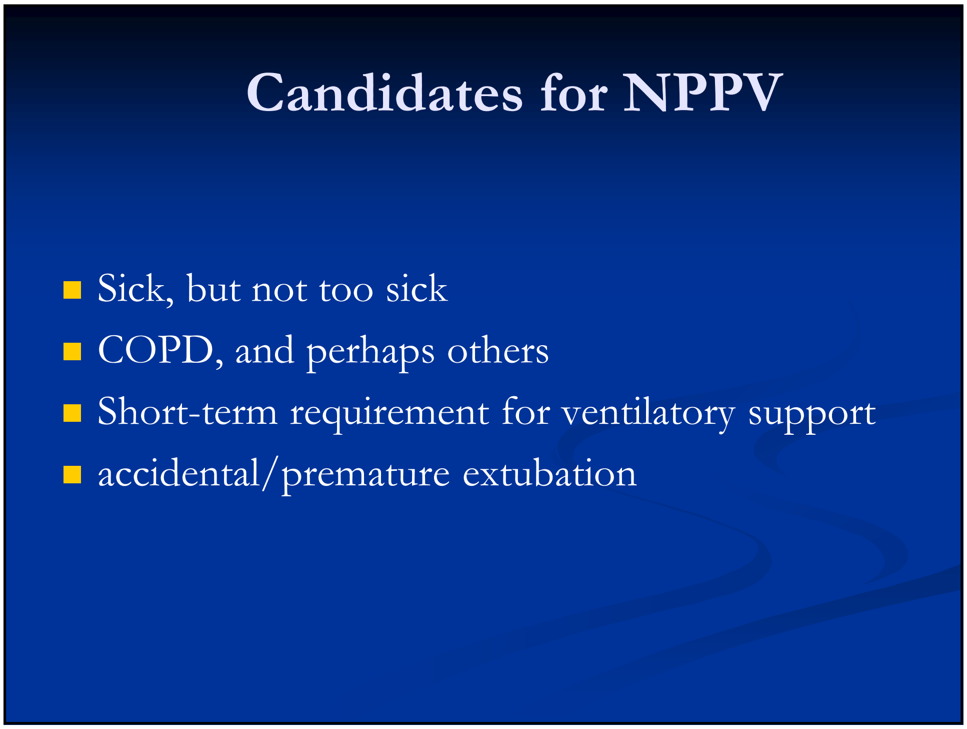
CONCLUSIONS
In patients with nonhypercapnic acute hypoxemic respiratory failure, treatment with high-flow oxygen, standard oxygen, or noninvasive ventilation did not result in significantly different intubation rates. There was a significant difference in favor of high-flow oxygen in 90-day mortality.

HFNC vs. NIV


19,528 Patients were admitted to the ICUs in the study period, February 2011–April 2013
4777 Had acute respiratory failure
2271 Were excluded
1366 Had acute or chronic lung disease
651 Had cardiogenic pulmonary edema
155 Had contraindications to noninvasive ventilation
99 Had administrative reasons
2506 Had acute hypoxemic respiratory failure
1981 Were excluded
647 Had shock or Glasgow Coma Scale score <12
582 Had hypercapnia (Paco₂ >45 mm Hg)
476 Had urgent need for intubation
180 Had do-not-intubate order
96 Had neutropenia
525 Were eligible for inclusion
212 Were excluded
160 Had logistic reasons
52 Declined to participate
313 Underwent randomization
106 Were assigned to high-flow–oxygen group
96 Were assigned to standard-oxygen group
111 Were assigned to non-invasive-ventilation group
2 Withdrew consent
1 Withdrew consent
310 Were included in the analysis and in the 90-day follow-up
106 Were in the high-flow–oxygen group
94 Were in the standard-oxygen group
110 Were in the noninvasive-ventilation group

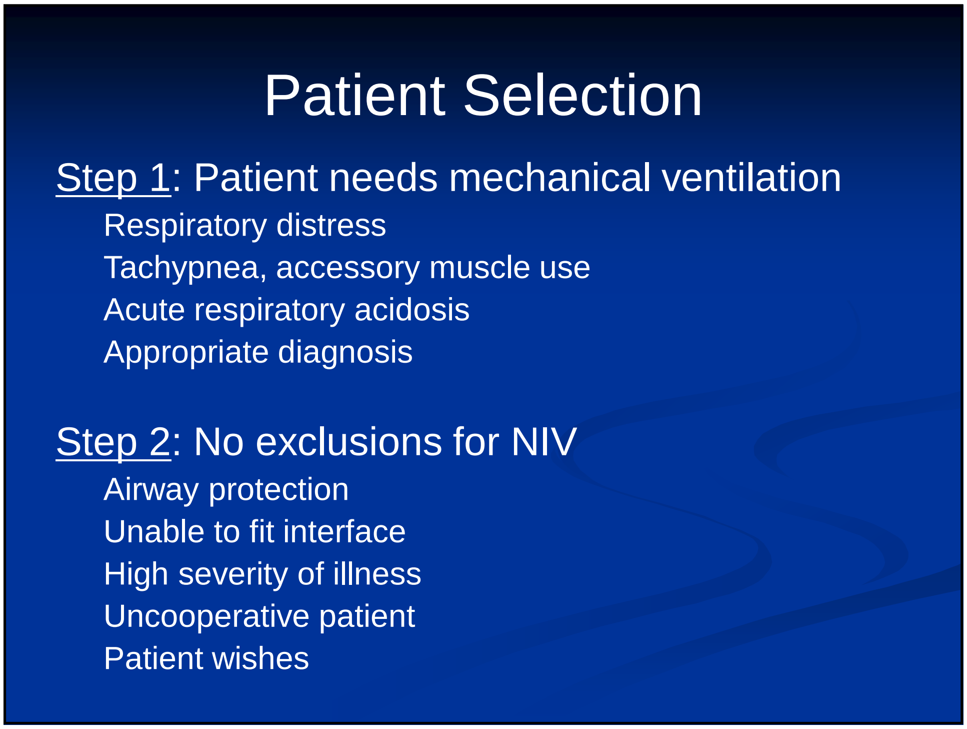
N Engl J Med 2015; 372:2185-96.


patient selection
NIV
clinician skills
equipment selection



Candidates for NPPV

- Sick, but not too sick
- COPD, and perhaps others
- Short-term requirement for ventilatory support
- accidental/premature extubation



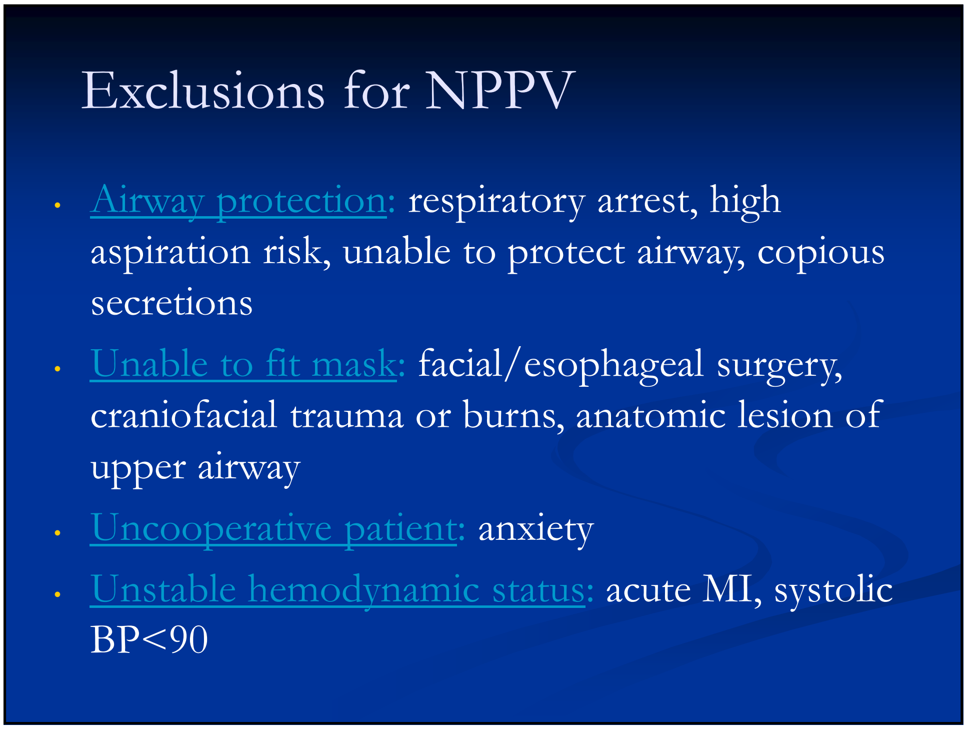
Patient Selection

Step 1: Patient needs mechanical ventilation

Respiratory distress
Tachypnea, accessory muscle use
Acute respiratory acidosis
Appropriate diagnosis

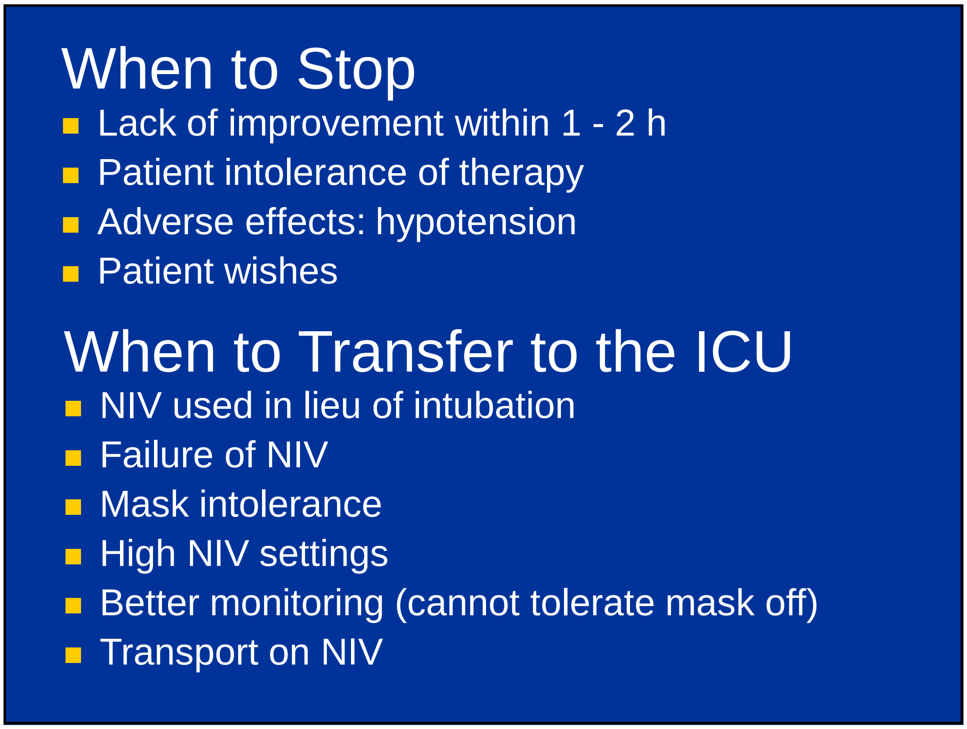
Step 2: No exclusions for NIV

Airway protection
Unable to fit interface
High severity of illness
Uncooperative patient
Patient wishes



Exclusions for NPPV

- Airway protection: respiratory arrest, high aspiration risk, unable to protect airway, copious secretions
- Unable to fit mask: facial/esophageal surgery, craniofacial trauma or burns, anatomic lesion of upper airway
- Uncooperative patient: anxiety
- Unstable hemodynamic status: acute MI, systolic BP<90

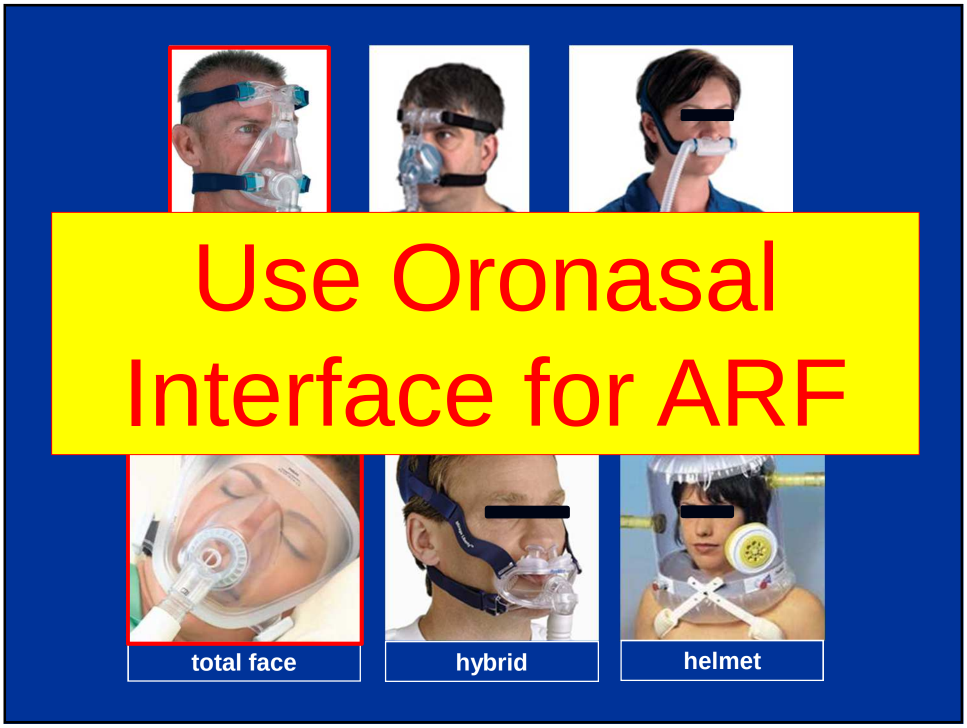


When to Stop

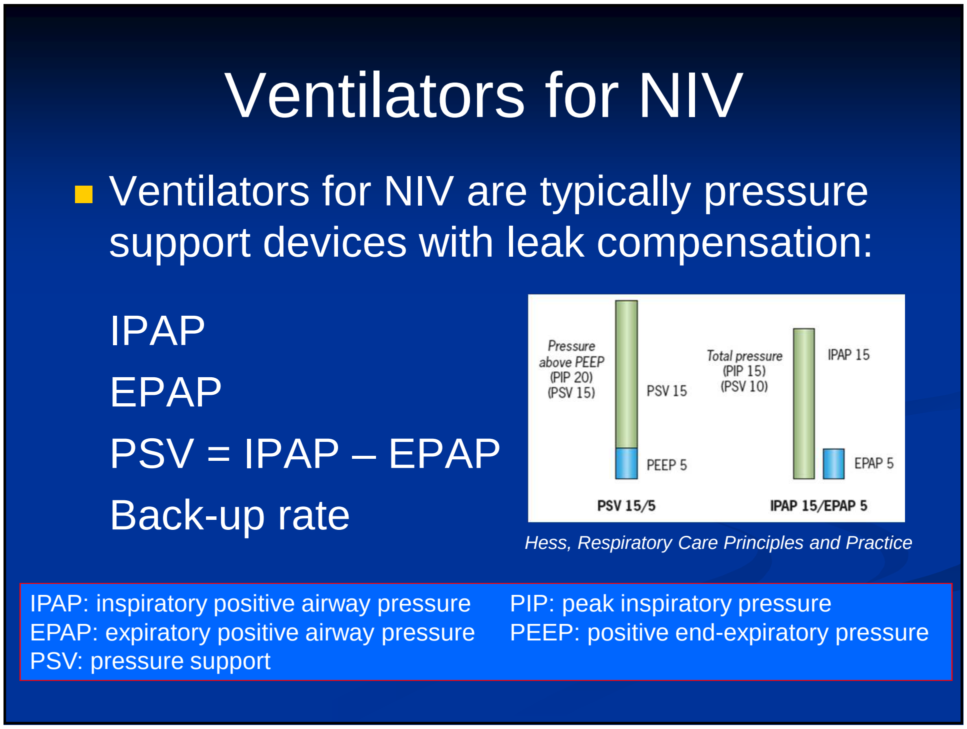
- Lack of improvement within 1 - 2 h
- Patient intolerance of therapy
- Adverse effects: hypotension
- Patient wishes

When to Transfer to the ICU

- NIV used in lieu of intubation
- Failure of NIV
- Mask intolerance
- High NIV settings
- Better monitoring (cannot tolerate mask off)
- Transport on NIV



Use Oronasal Interface for ARF



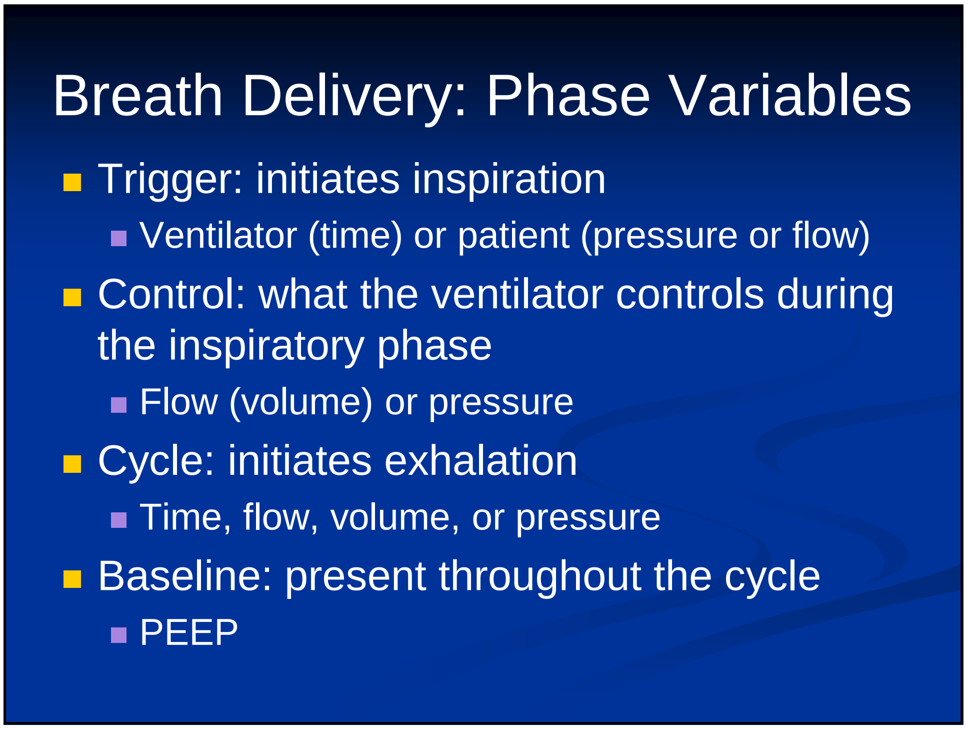
Ventilators for NIV

- Ventilators for NIV are typically pressure support devices with leak compensation:

IPAP
EPAP
PSV = IPAP – EPAP
Back-up rate

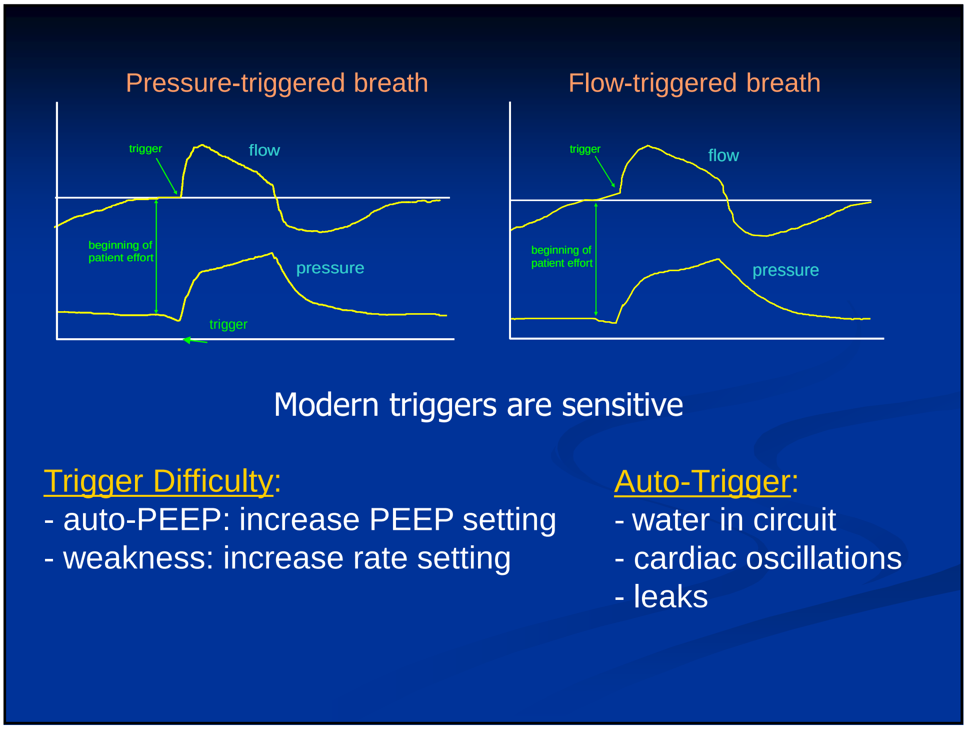
Hess, Respiratory Care Principles and Practice

IPAP: inspiratory positive airway pressure
EPAP: expiratory positive airway pressure
PSV: pressure support
PIP: peak inspiratory pressure
PEEP: positive end-expiratory pressure



Breath Delivery: Phase Variables

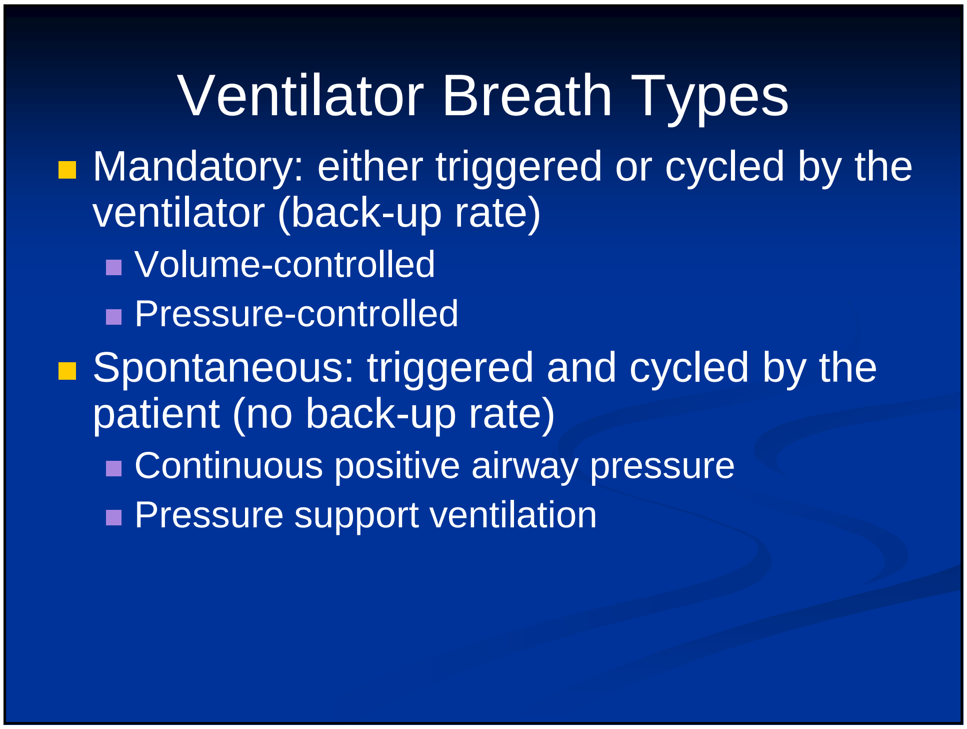
- Trigger: initiates inspiration
  - Ventilator (time) or patient (pressure or flow)
- Control: what the ventilator controls during the inspiratory phase
  - Flow (volume) or pressure
- Cycle: initiates exhalation
  - Time, flow, volume, or pressure
- Baseline: present throughout the cycle
  - PEEP



Modern triggers are sensitive

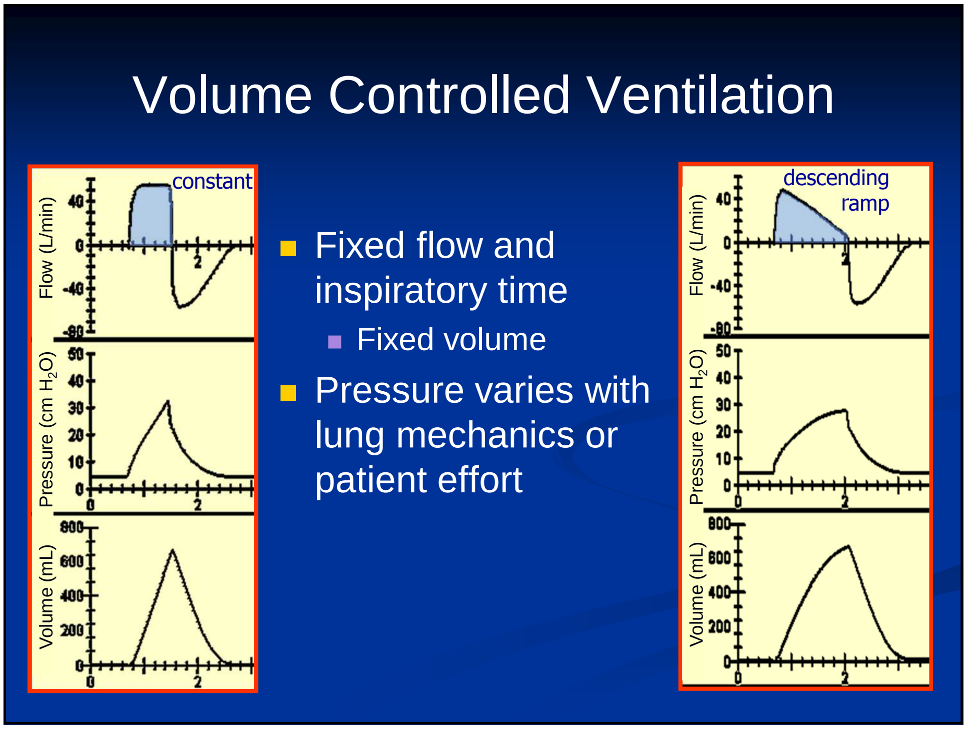
Trigger Difficulty:
- auto-PEEP: increase PEEP setting
- weakness: increase rate setting

Auto-Trigger:
- water in circuit
- cardiac oscillations
- leaks



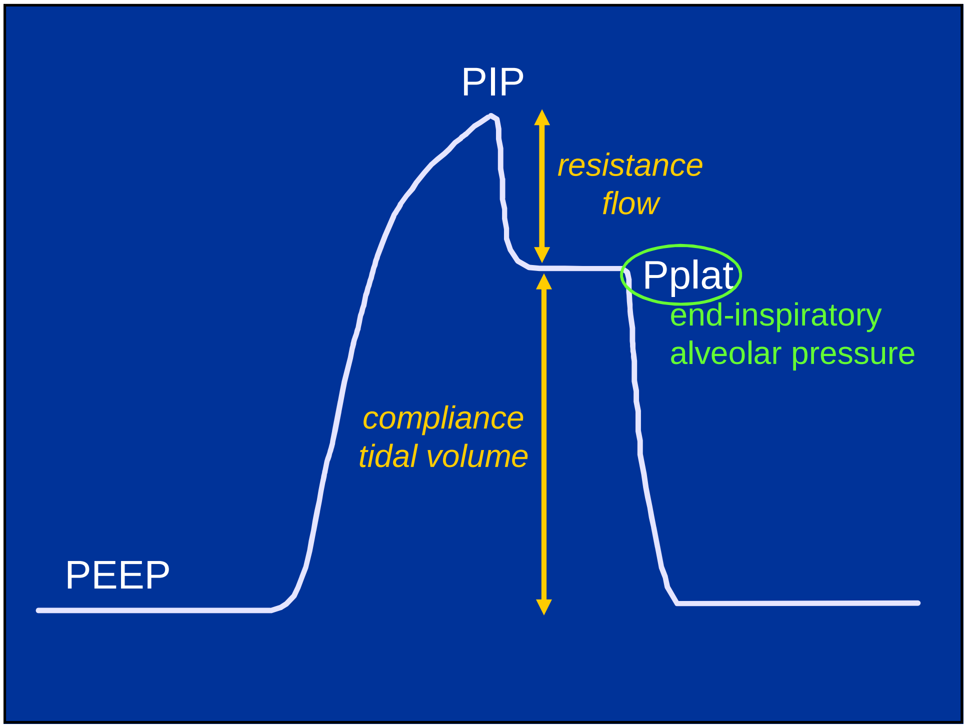
Ventilator Breath Types

- Mandatory: either triggered or cycled by the ventilator (back-up rate)
  - Volume-controlled
  - Pressure-controlled
- Spontaneous: triggered and cycled by the patient (no back-up rate)
  - Continuous positive airway pressure
  - Pressure support ventilation



Volume Controlled Ventilation

- Fixed flow and inspiratory time
  - Fixed volume
- Pressure varies with lung mechanics or patient effort



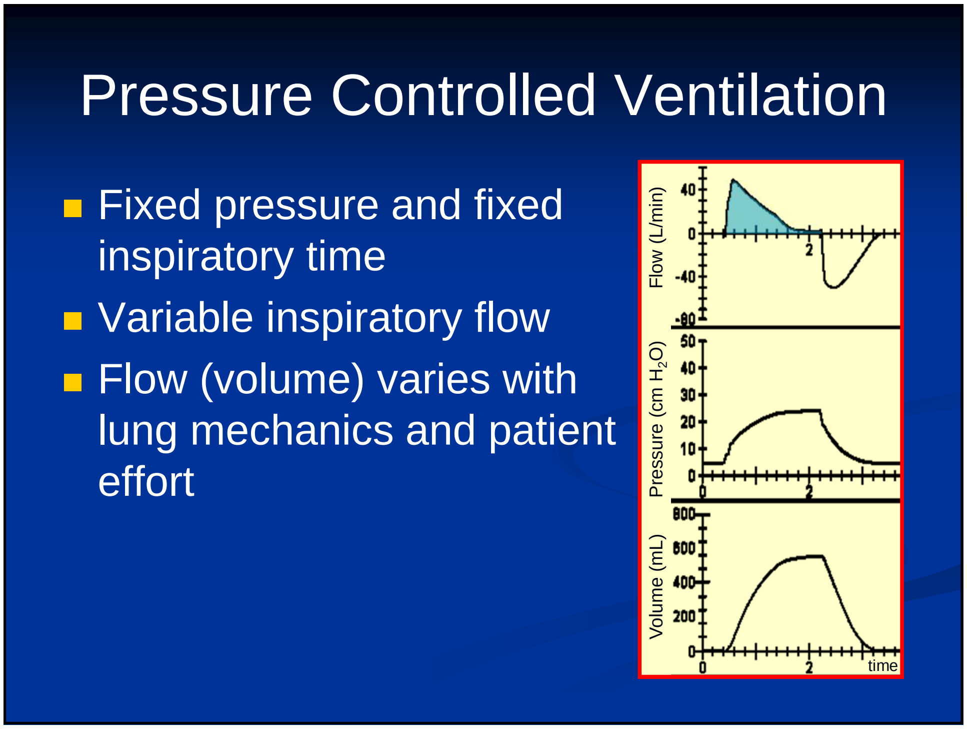
PIP

resistance
flow

Pplat
end-inspiratory
alveolar pressure

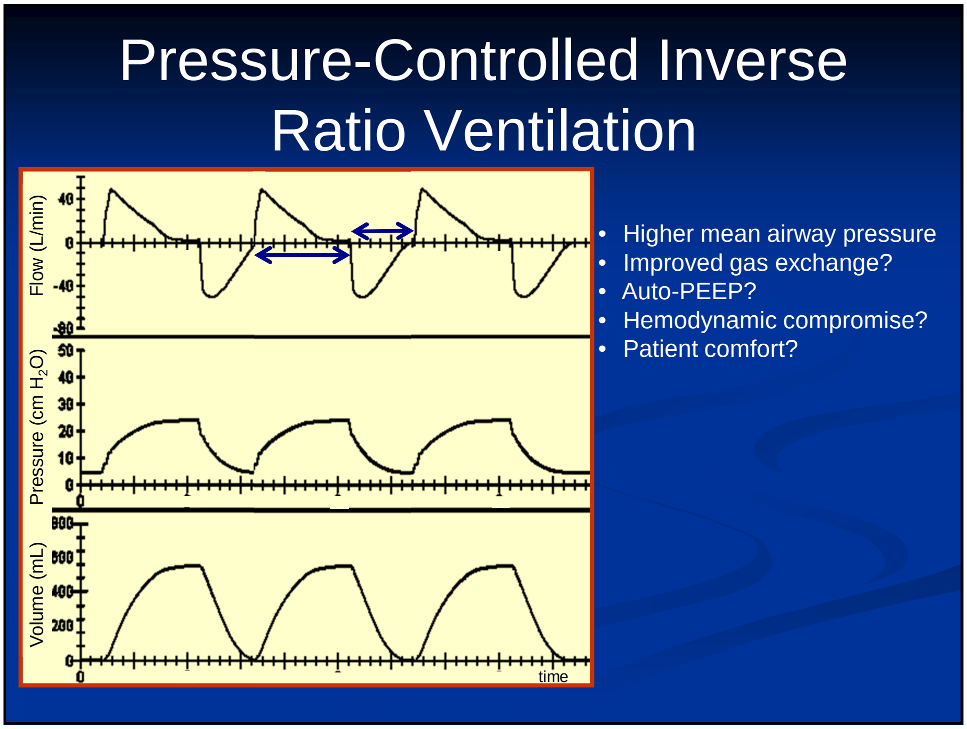
compliance
tidal volume

PEEP



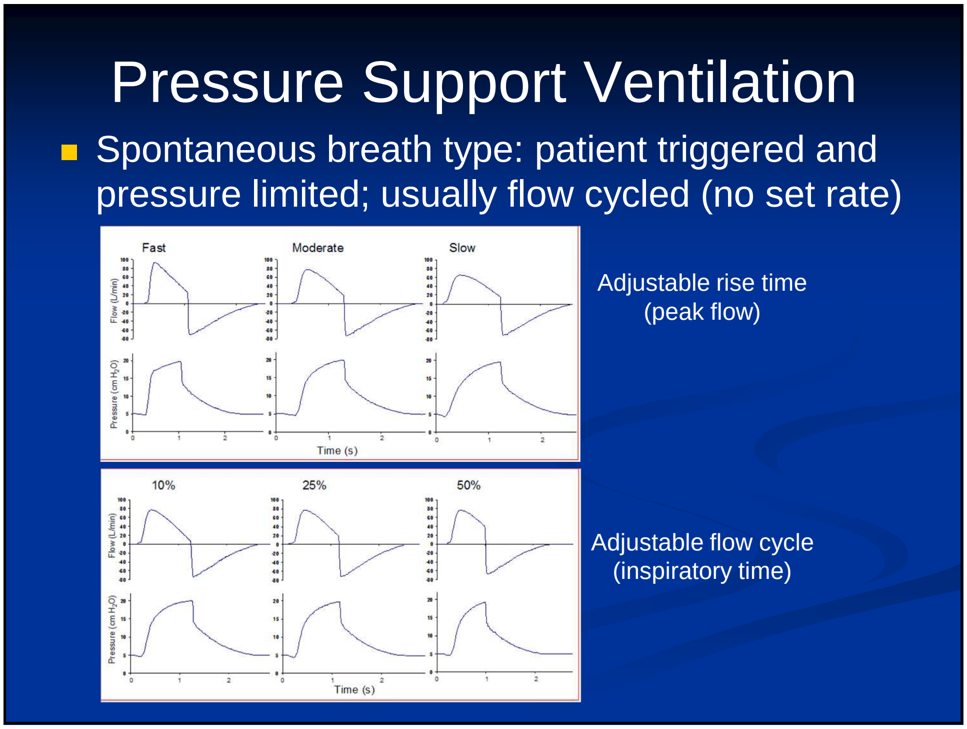
Pressure Controlled Ventilation

- Fixed pressure and fixed inspiratory time
- Variable inspiratory flow
- Flow (volume) varies with lung mechanics and patient effort



Pressure-Controlled Inverse Ratio Ventilation

- Higher mean airway pressure
- Improved gas exchange?
- Auto-PEEP?
- Hemodynamic compromise?
- Patient comfort?

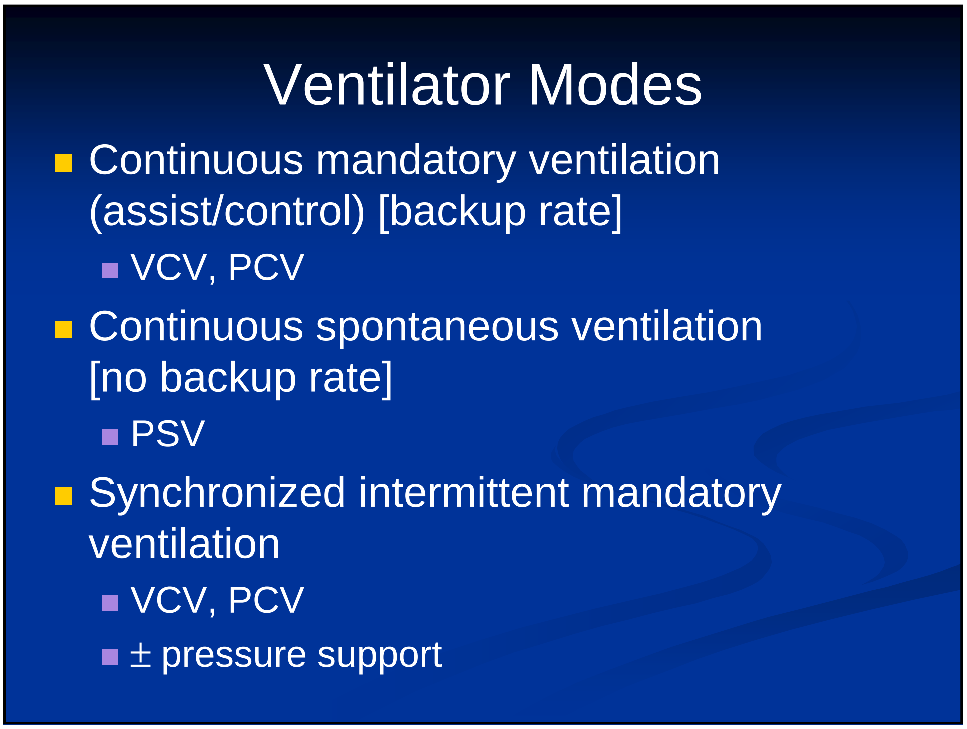


Pressure Support Ventilation

- Spontaneous breath type: patient triggered and pressure limited; usually flow cycled (no set rate)

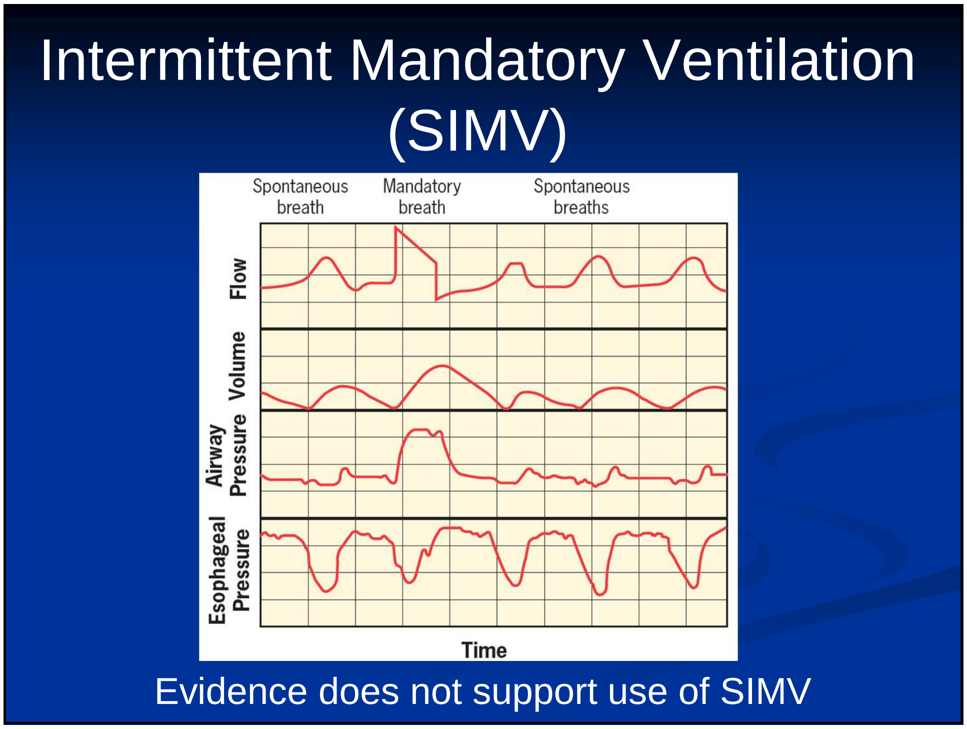
Adjustable rise time (peak flow)

Adjustable flow cycle (inspiratory time)



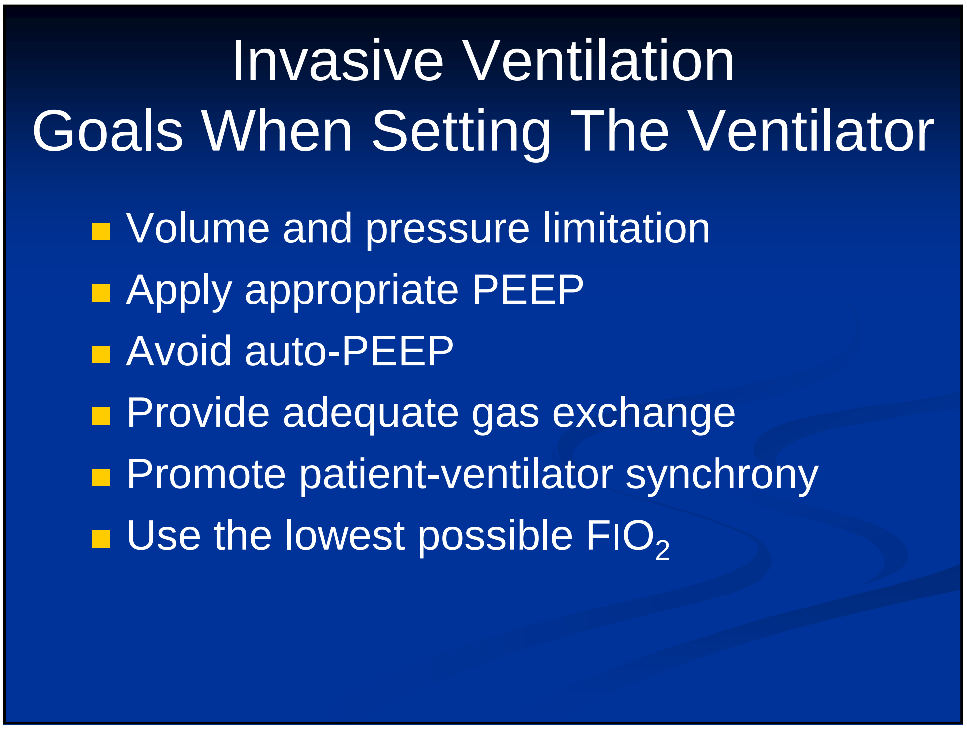
Ventilator Modes

- Continuous mandatory ventilation (assist/control) [backup rate]
  - VCV, PCV
- Continuous spontaneous ventilation [no backup rate]
  - PSV
- Synchronized intermittent mandatory ventilation
  - VCV, PCV
  - ± pressure support



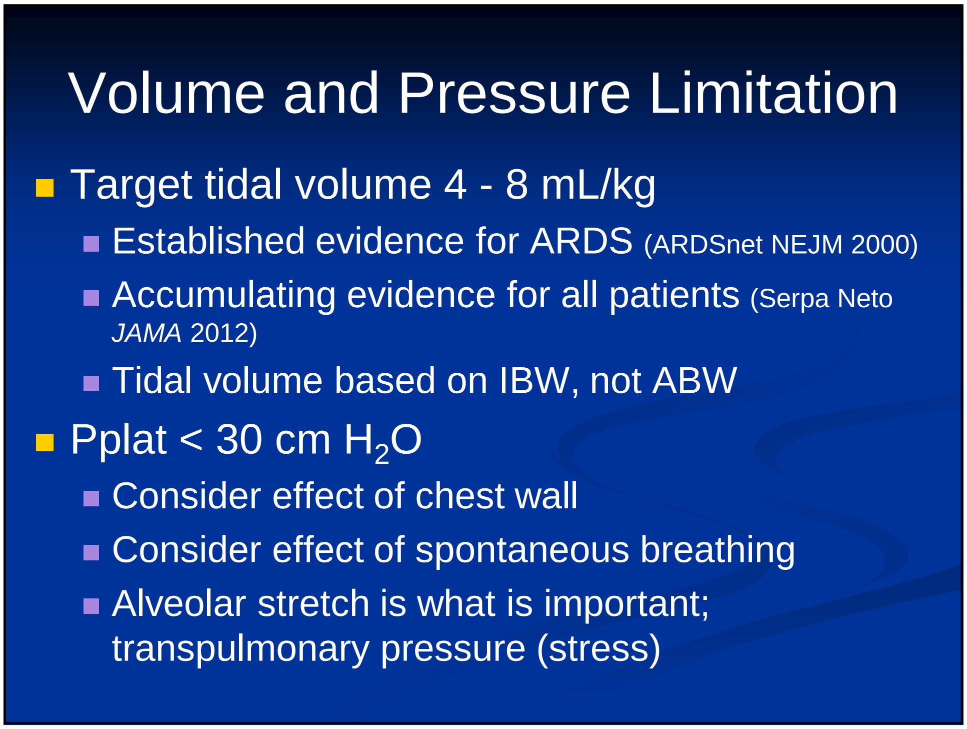
Intermittent Mandatory Ventilation (SIMV)

Evidence does not support use of SIMV



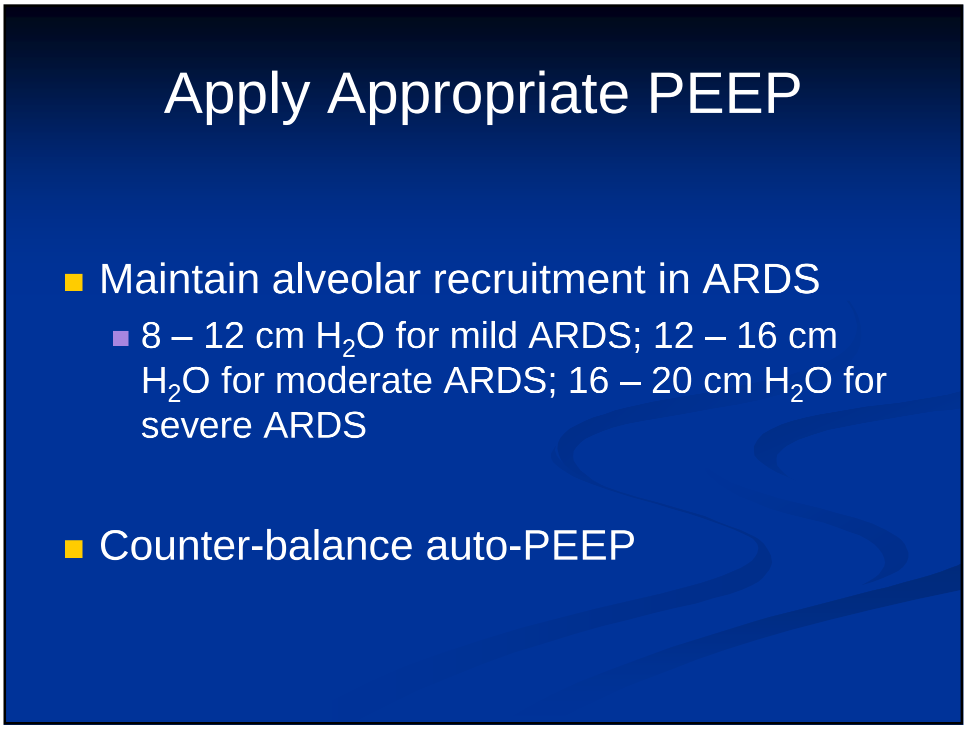
Invasive Ventilation
Goals When Setting The Ventilator

- Volume and pressure limitation
- Apply appropriate PEEP
- Avoid auto-PEEP
- Provide adequate gas exchange
- Promote patient-ventilator synchrony
- Use the lowest possible FIO_2



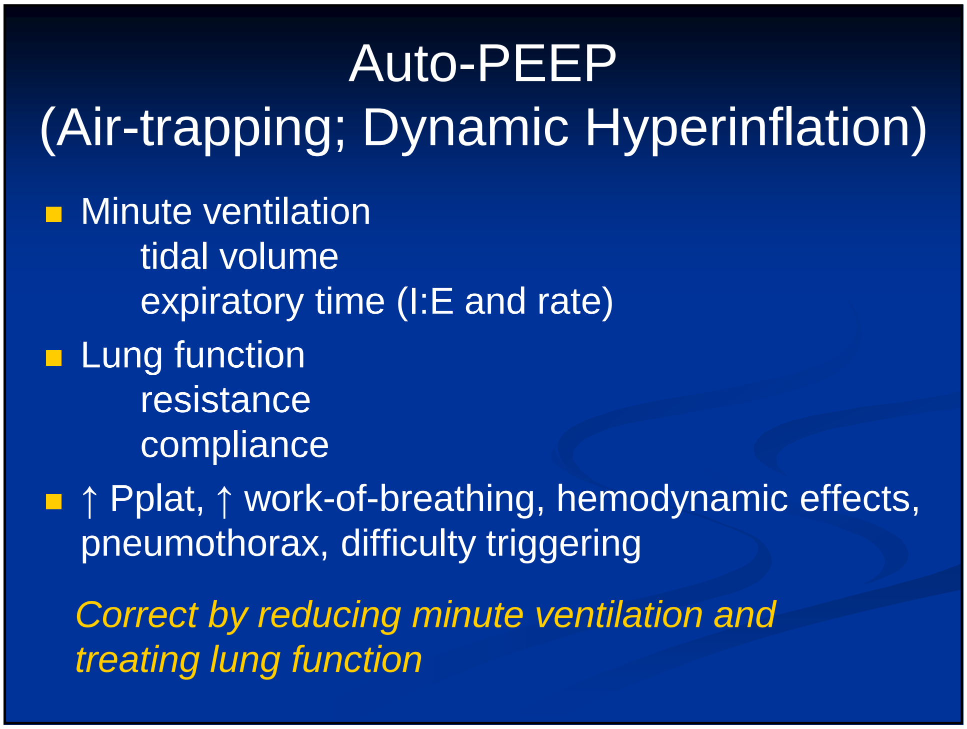
Volume and Pressure Limitation

- Target tidal volume 4 - 8 mL/kg
  - Established evidence for ARDS (ARDSnet NEJM 2000)
  - Accumulating evidence for all patients (Serpa Neto *JAMA* 2012)
  - Tidal volume based on IBW, not ABW
- Pplat < 30 cm H_2O
  - Consider effect of chest wall
  - Consider effect of spontaneous breathing
  - Alveolar stretch is what is important; transpulmonary pressure (stress)



Apply Appropriate PEEP

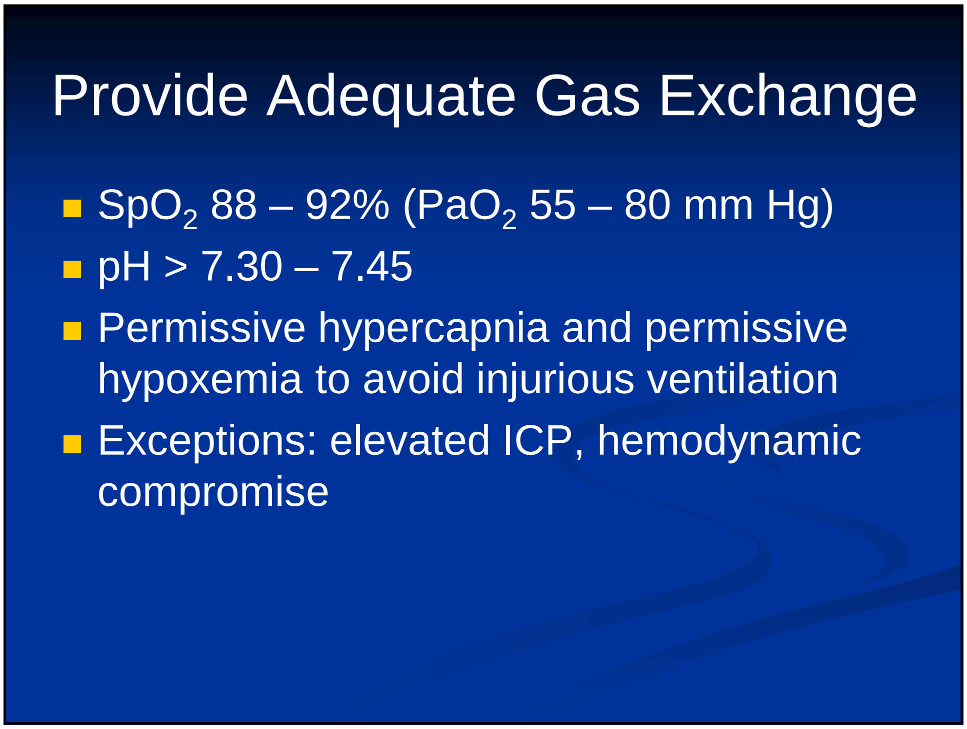
- Maintain alveolar recruitment in ARDS
  - 8 – 12 cm H_2O for mild ARDS; 12 – 16 cm H_2O for moderate ARDS; 16 – 20 cm H_2O for severe ARDS
- Counter-balance auto-PEEP



Auto-PEEP
(Air-trapping; Dynamic Hyperinflation)

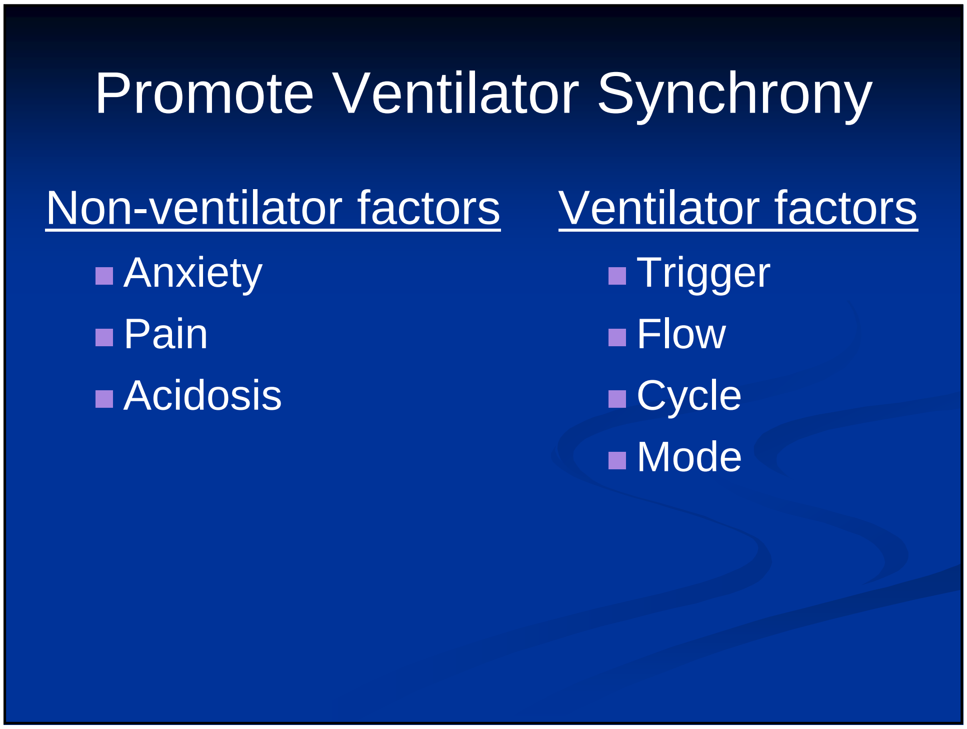
- Minute ventilation
  - tidal volume
  - expiratory time (I:E and rate)
- Lung function
  - resistance
  - compliance
- ↑ Pplat, ↑ work-of-breathing, hemodynamic effects, pneumothorax, difficulty triggering

Correct by reducing minute ventilation and treating lung function



Provide Adequate Gas Exchange

- SpO_2 88 – 92% (PaO_2 55 – 80 mm Hg)
- pH > 7.30 – 7.45
- Permissive hypercapnia and permissive hypoxemia to avoid injurious ventilation
- Exceptions: elevated ICP, hemodynamic compromise



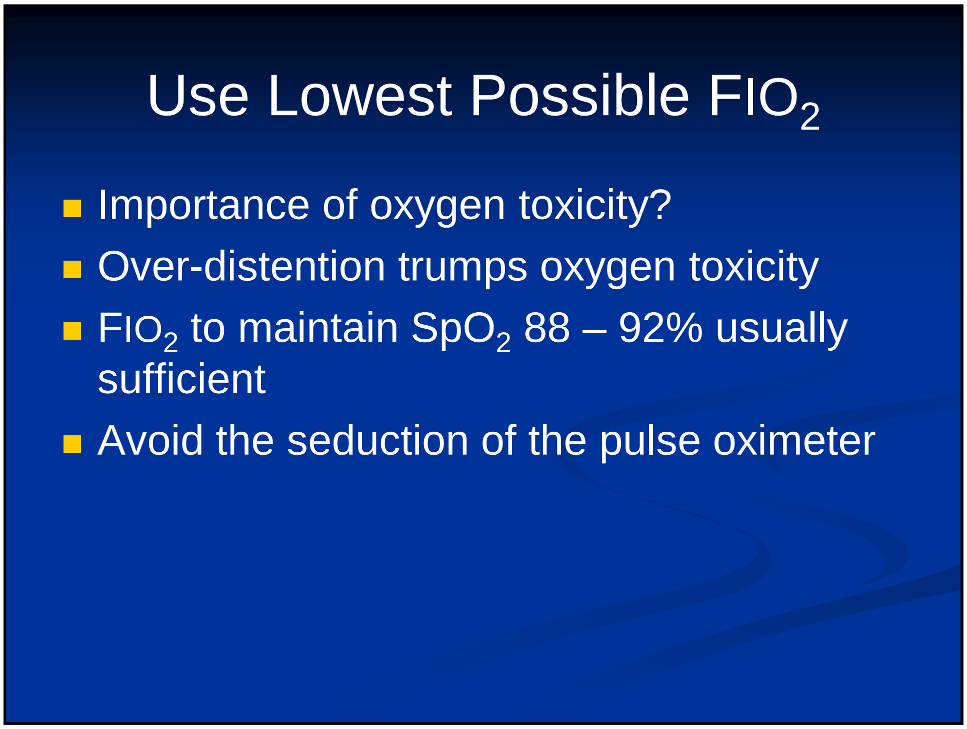
Promote Ventilator Synchrony

Non-ventilator factors

- Anxiety
- Pain
- Acidosis

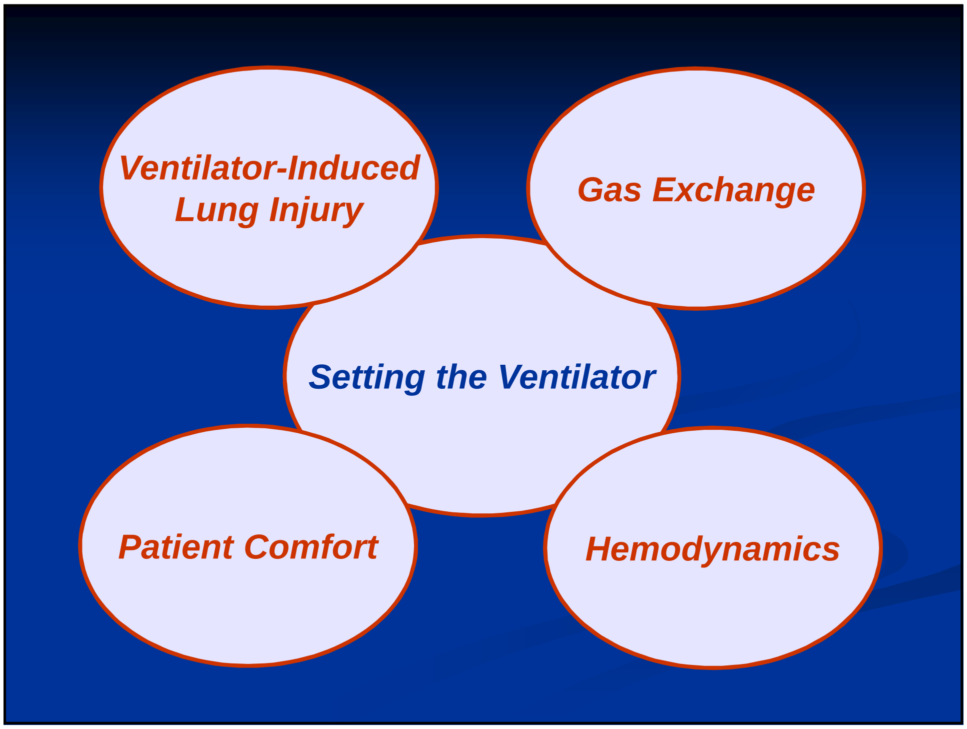
Ventilator factors

- Trigger
- Flow
- Cycle
- Mode



Use Lowest Possible FIO_2

- Importance of oxygen toxicity?
- Over-distention trumps oxygen toxicity
- FIO_2 to maintain SpO_2 88 – 92% usually sufficient
- Avoid the seduction of the pulse oximeter



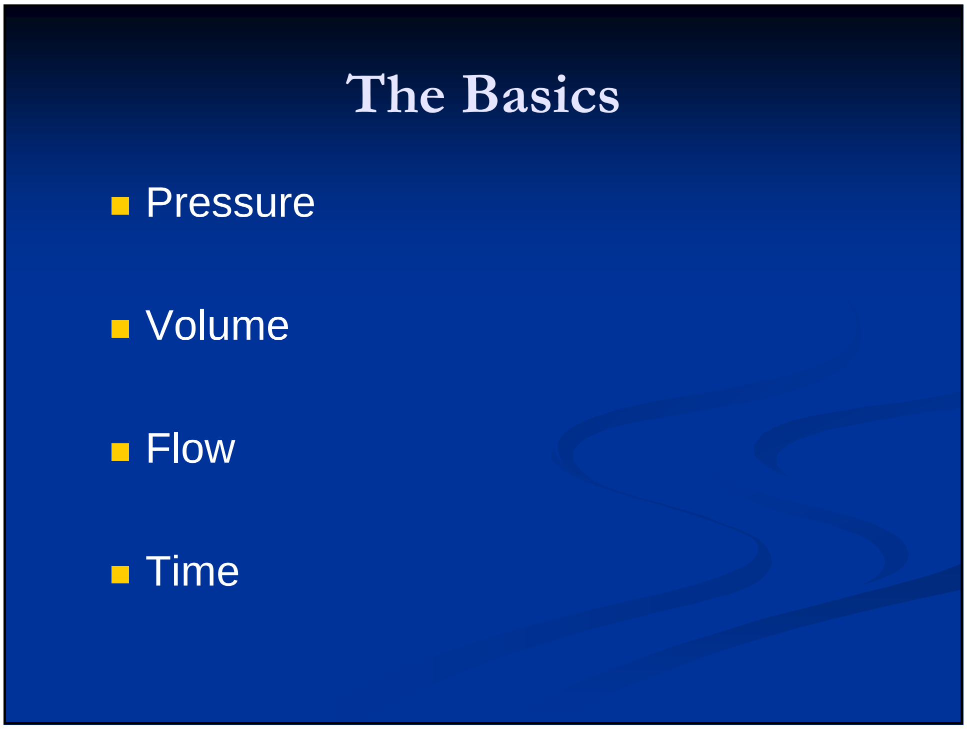
Setting the Ventilator

Ventilator-Induced Lung Injury

Gas Exchange

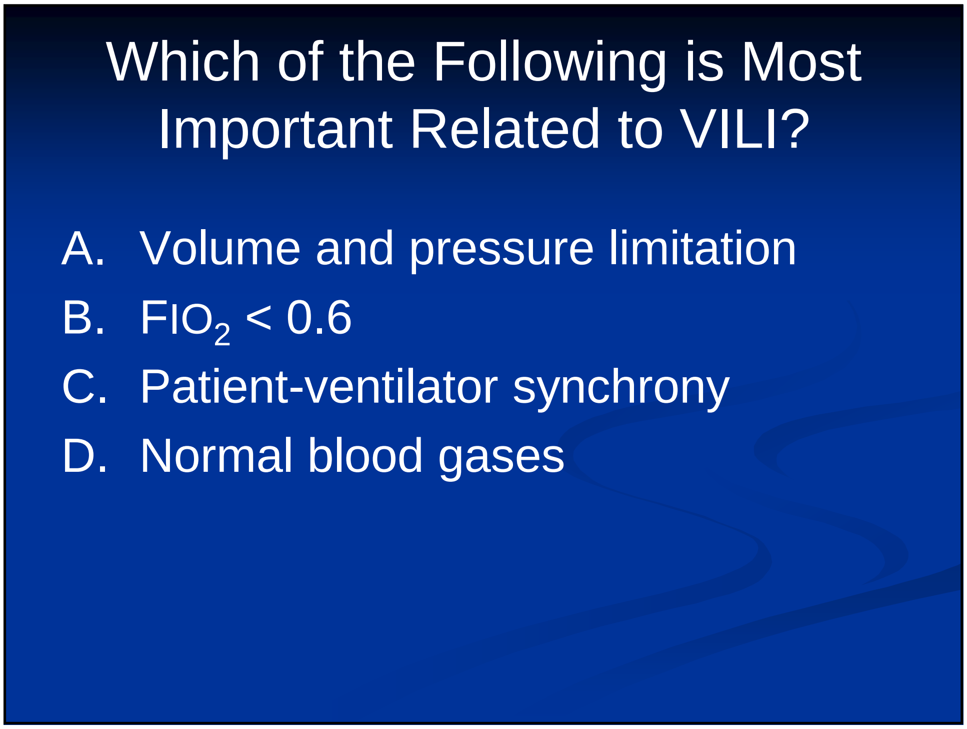
Patient Comfort

Hemodynamics



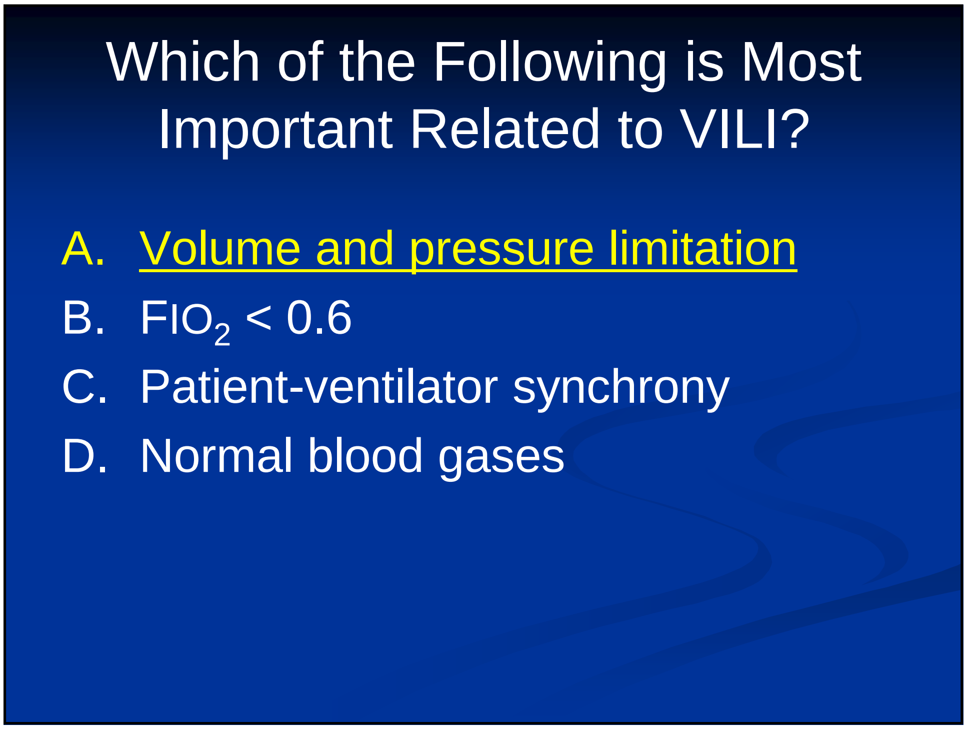
The Basics

- Pressure
- Volume
- Flow
- Time



Which of the Following is Most Important Related to VILI?

A. Volume and pressure limitation
B. $FIO_2 < 0.6$
C. Patient-ventilator synchrony
D. Normal blood gases



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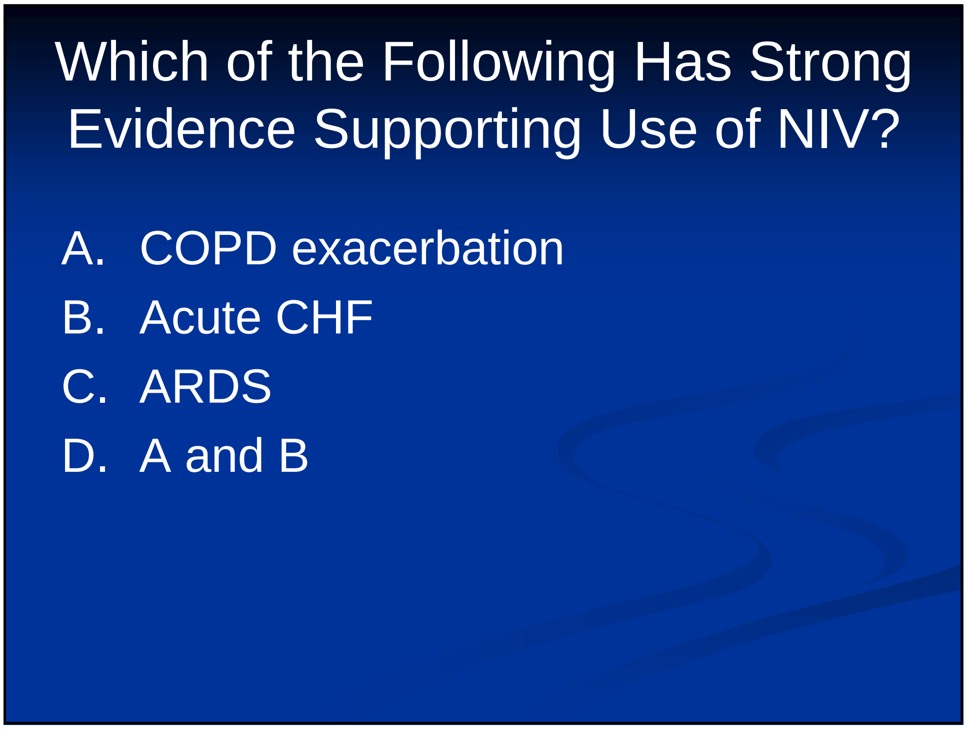
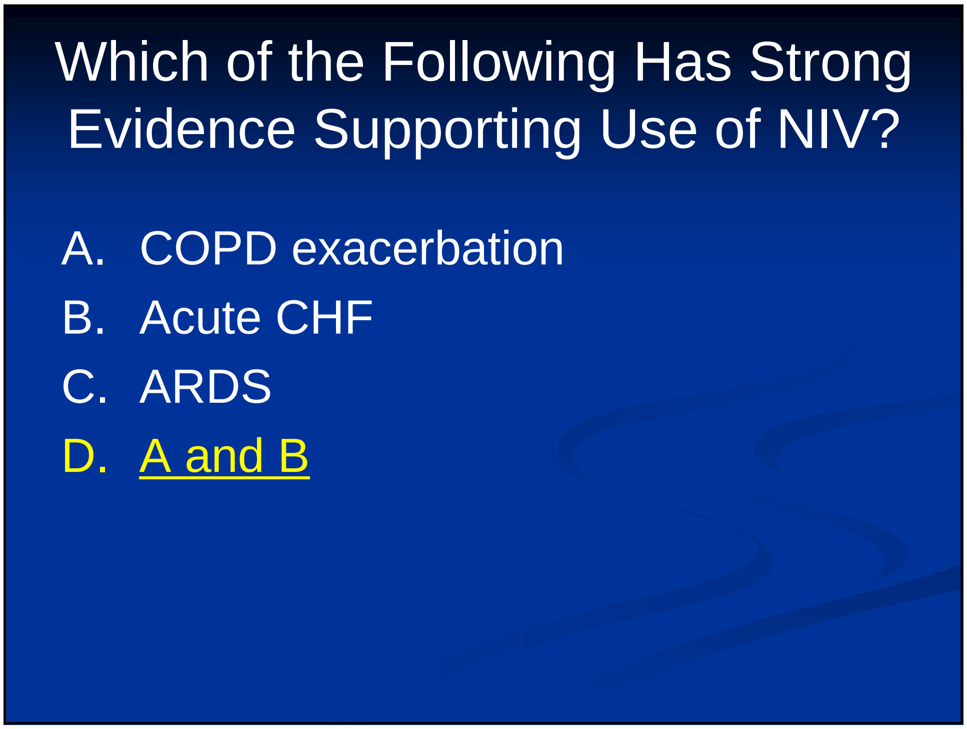


Which of the Following Has Strong Evidence Supporting Use of NIV?

A. COPD exacerbation
B. Acute CHF
C. ARDS
D. A and B



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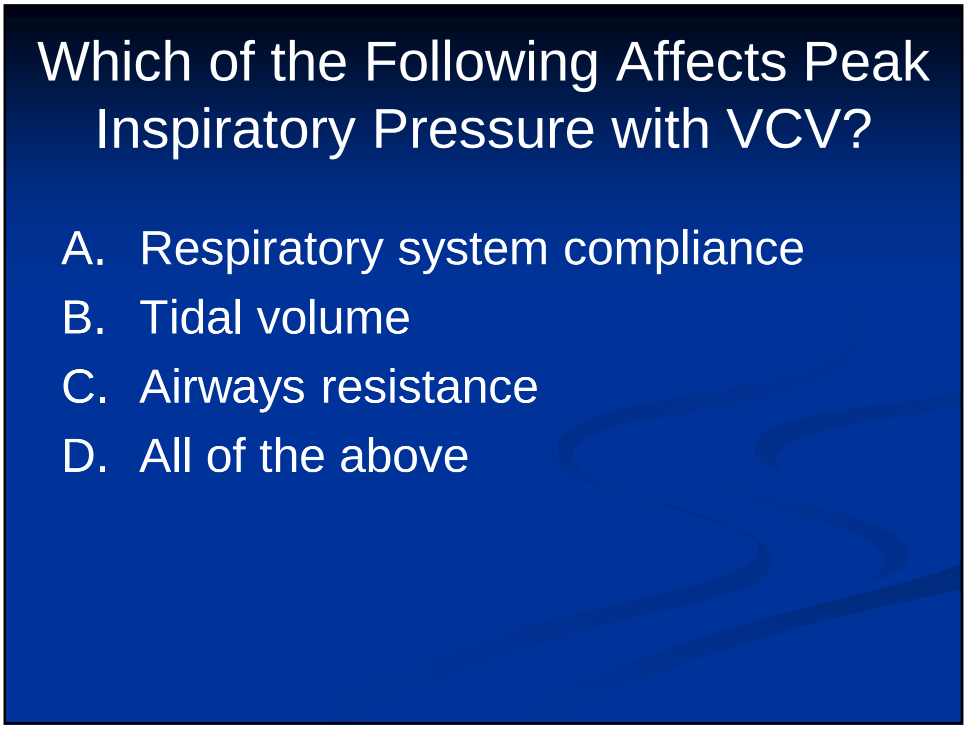
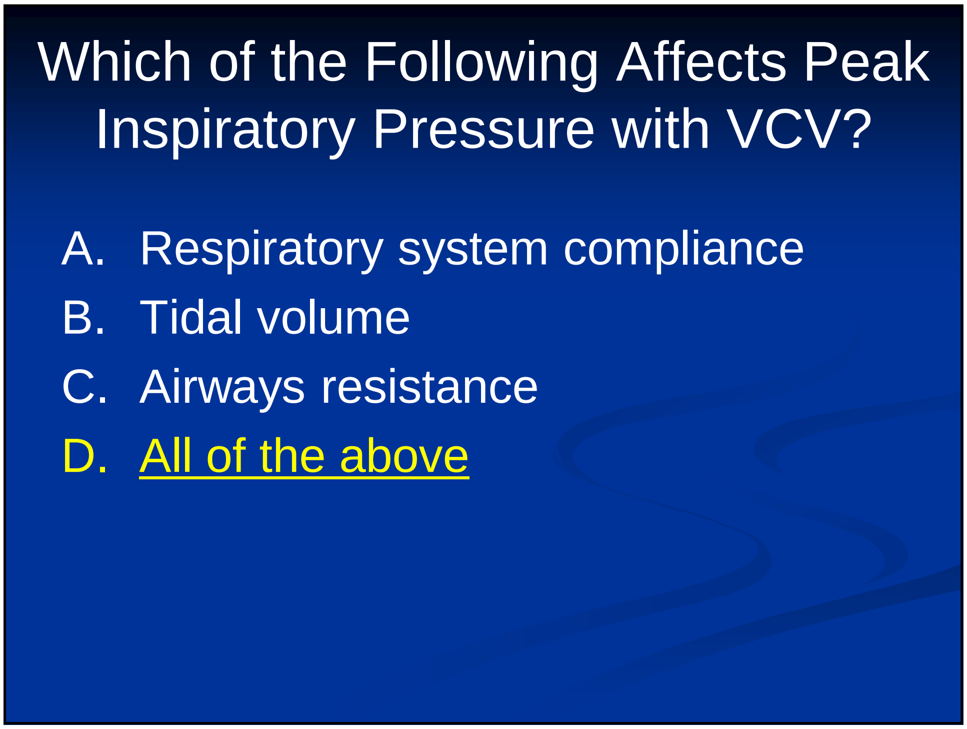


Which of the Following Affects Peak Inspiratory Pressure with VCV?

A. Respiratory system compliance
B. Tidal volume
C. Airways resistance
D. All of the above



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References

1. Keenan SP, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ 2011;183:E195-214.
2. Frat JP, et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. NEJM 2015;372:2185-96.
3. Mireles-Cabodevila E, et al. Alternative modes of mechanical ventilation: a review for the hospitalist. Cleve Clin J Med 2009;76:417-430.
4. Serpa Neto, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA 2012;308:1651-1659.
5. Hess DR. Approaches to conventional mechanical ventilation of the patient with acute respiratory distress syndrome. Respir Care 2011;56:1555-1572.

Paul F. Nuccio, MS, RRT, FAARC Disclosures

- None to report

Mechanical Ventilation: Liberation: The ABCDEF Bundle

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Associate Physician Medicine
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Instructor of Medicine

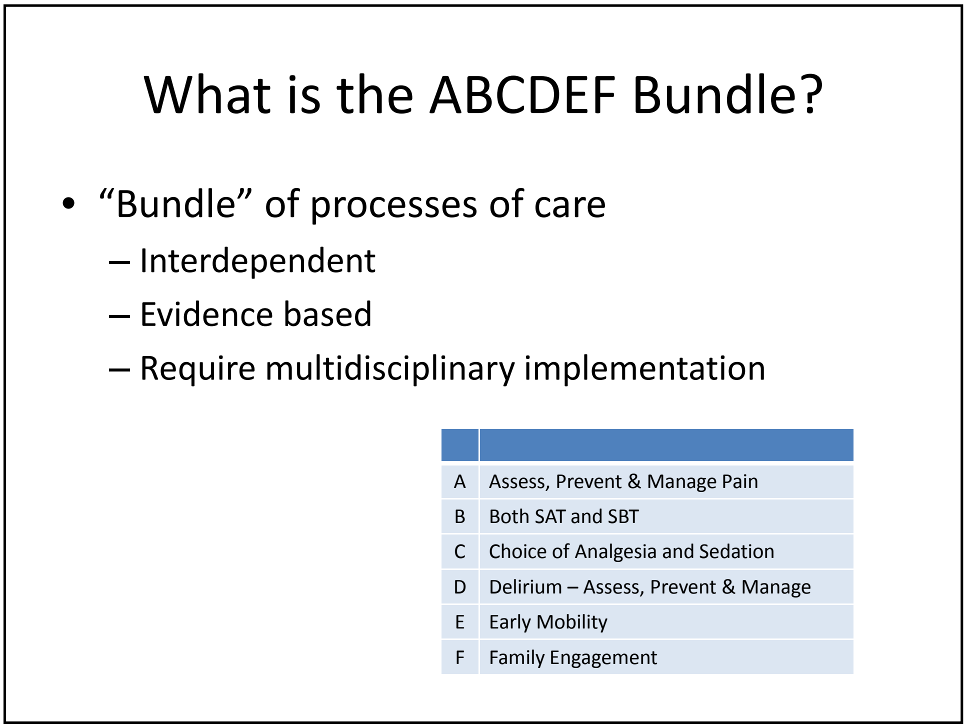
Disclosures

- No disclosures to report

Outline

- What is the ABCDEF Bundle?
  - Individual elements
  - Aggregate
- Why implement the ABCDEF Bundle / goals?
- Elements of the Bundle
  - What does it mean to implement the element?
  - Data to demonstrate improvement in patient care
- What is the impact of effective adoption of the bundle?

A	Assess, Prevent & Manage Pain
B	Both SAT and SBT
C	Choice of Analgesia and Sedation
D	Delirium – Assess, Prevent & Manage
E	Early Mobility
F	Family Engagement



What is the ABCDEF Bundle?

- “Bundle” of processes of care
  - Interdependent
  - Evidence based
  - Require multidisciplinary implementation

A	Assess, Prevent & Manage Pain
B	Both SAT and SBT
C	Choice of Analgesia and Sedation
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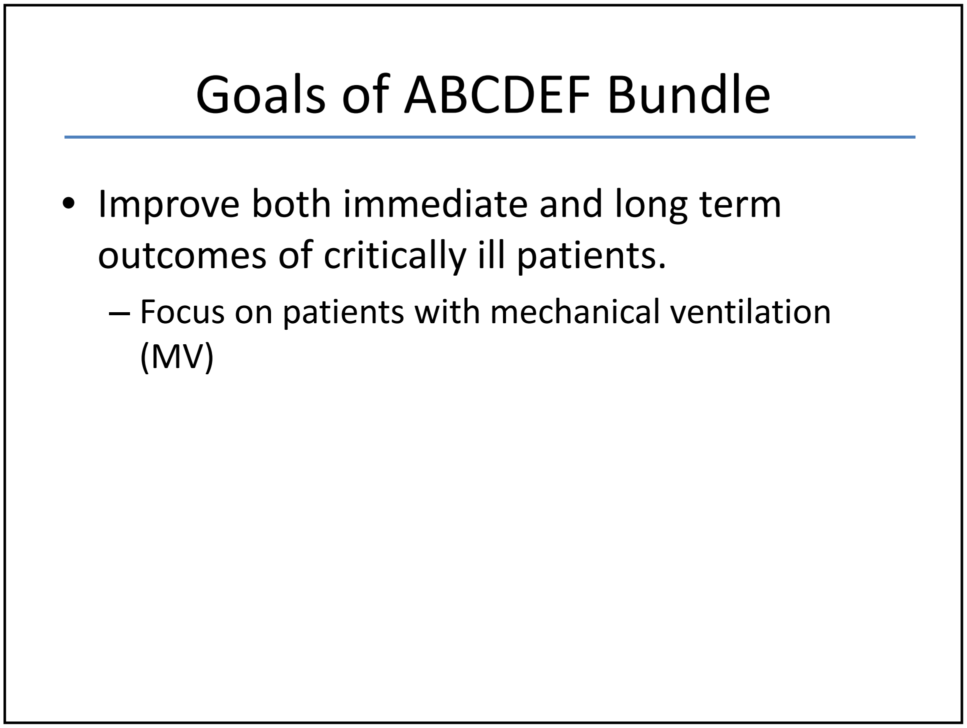
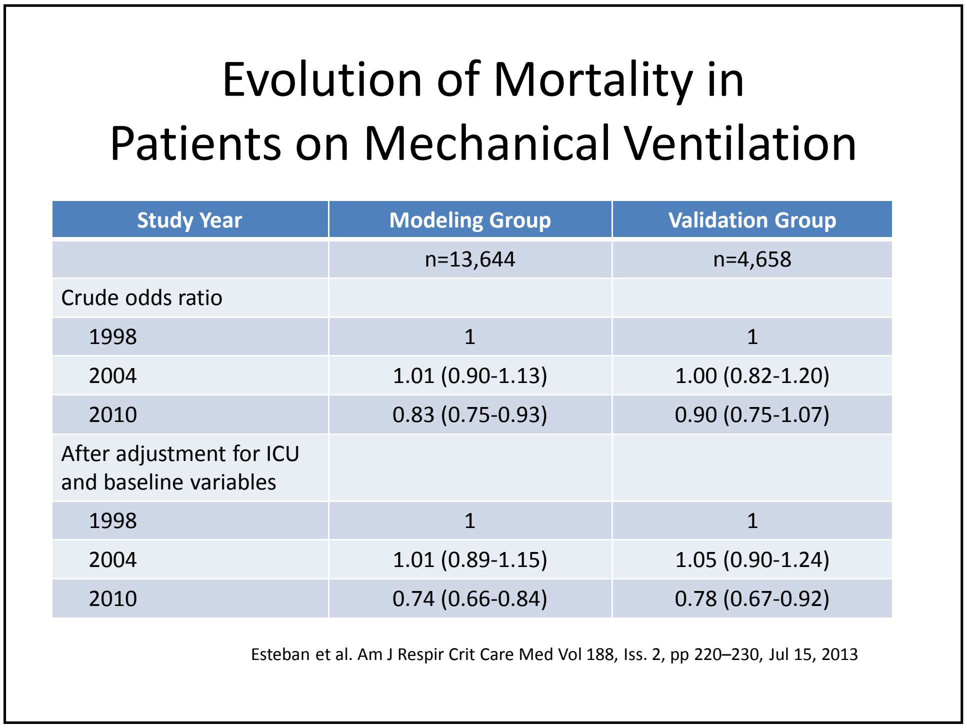
E	Early Mobility
F	Family Engagement



Goals of ABCDEF Bundle

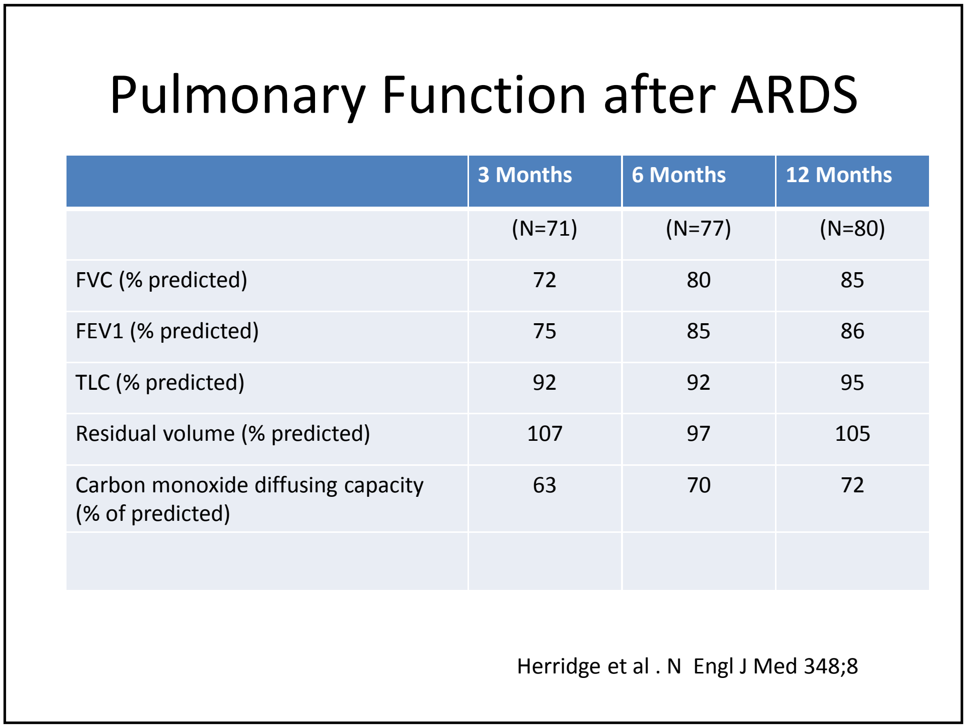
- Improve both immediate and long term outcomes of critically ill patients.
  - Focus on patients with mechanical ventilation (MV)



Evolution of Mortality in Patients on Mechanical Ventilation

Study Year	Modeling Group	Validation Group
	n=13,644	n=4,658
Crude odds ratio		
1998	1	1
2004	1.01 (0.90-1.13)	1.00 (0.82-1.20)
2010	0.83 (0.75-0.93)	0.90 (0.75-1.07)
After adjustment for ICU and baseline variables		
1998	1	1
2004	1.01 (0.89-1.15)	1.05 (0.90-1.24)
2010	0.74 (0.66-0.84)	0.78 (0.67-0.92)

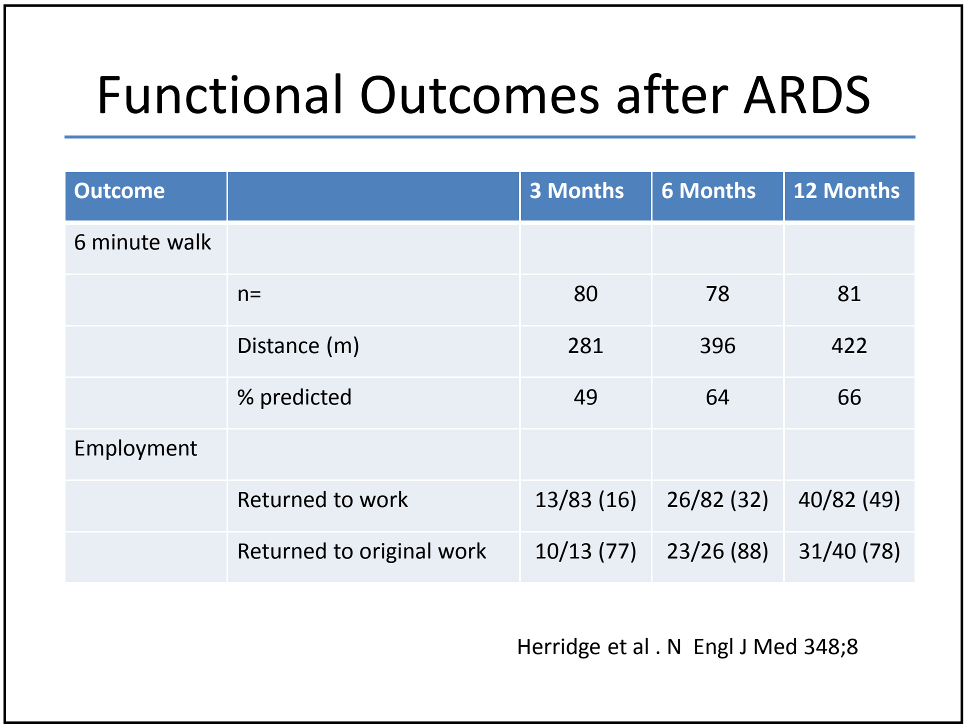
Esteban et al. Am J Respir Crit Care Med Vol 188, Iss. 2, pp 220–230, Jul 15, 2013



Pulmonary Function after ARDS

	3 Months	6 Months	12 Months
	(N=71)	(N=77)	(N=80)
FVC (% predicted)	72	80	85
FEV1 (% predicted)	75	85	86
TLC (% predicted)	92	92	95
Residual volume (% predicted)	107	97	105
Carbon monoxide diffusing capacity (% of predicted)	63	70	72

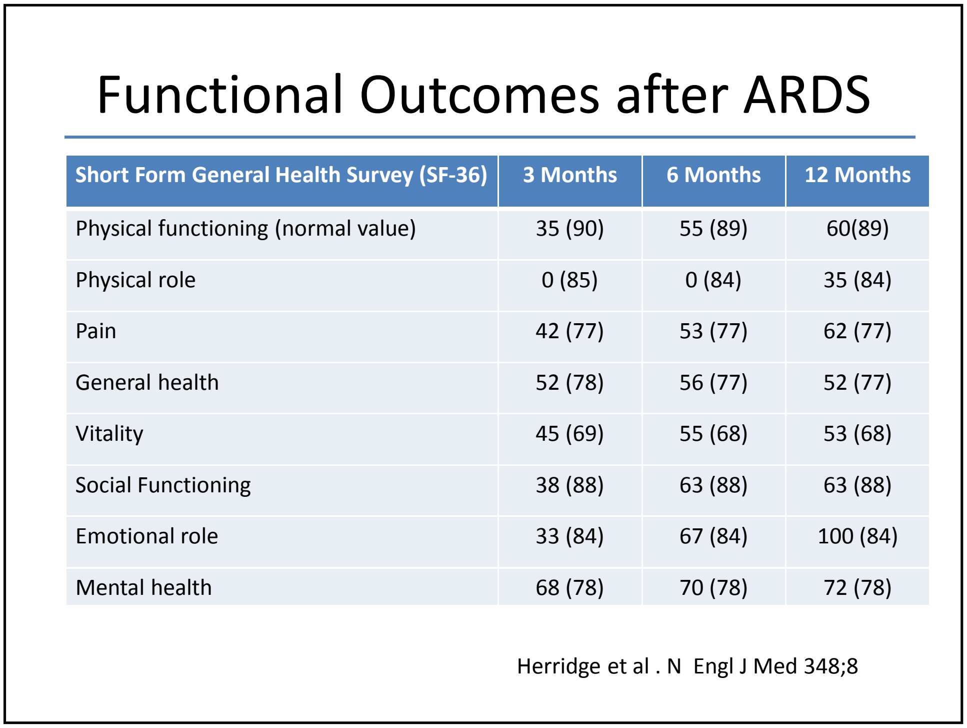
Herridge et al . N Engl J Med 348;8



Functional Outcomes after ARDS

Outcome		3 Months	6 Months	12 Months
6 minute walk				
	n=	80	78	81
	Distance (m)	281	396	422
	% predicted	49	64	66
Employment				
	Returned to work	13/83 (16)	26/82 (32)	40/82 (49)
	Returned to original work	10/13 (77)	23/26 (88)	31/40 (78)

Herridge et al . N Engl J Med 348;8



Functional Outcomes after ARDS

Short Form General Health Survey (SF-36)	3 Months	6 Months	12 Months
Physical functioning (normal value)	35 (90)	55 (89)	60(89)
Physical role	0 (85)	0 (84)	35 (84)
Pain	42 (77)	53 (77)	62 (77)
General health	52 (78)	56 (77)	52 (77)
Vitality	45 (69)	55 (68)	53 (68)
Social Functioning	38 (88)	63 (88)	63 (88)
Emotional role	33 (84)	67 (84)	100 (84)
Mental health	68 (78)	70 (78)	72 (78)

Herridge et al . N Engl J Med 348;8

ICU Care Impacts Long Term Outcomes

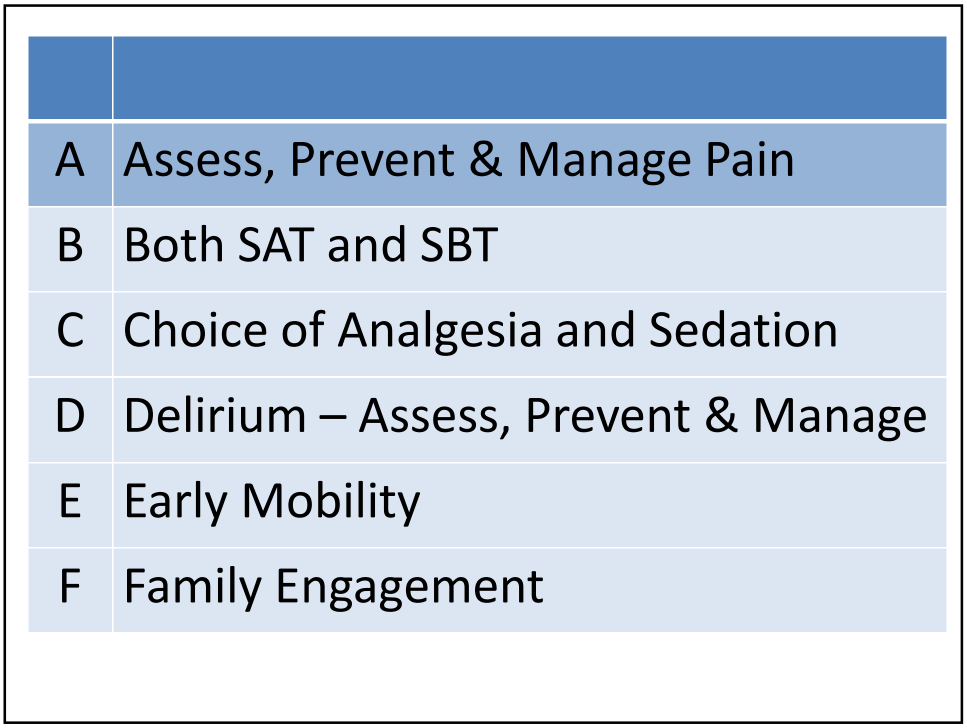
- Physical
- Cognitive
- Psychiatric
  - Depression
  - Post Traumatic Stress Disorder

Goals of ABCDEF Bundle

- Short term outcomes
  - Reduce delirium
  - Reduce MV days
  - Reduce ICU and hospital LOS
  - Decrease mortality
  - Improve functional status at d/c hospital
- Long term outcomes
  - Reduce sequela of Post ICU Syndrome.

- Support implementation of 2013 Clinical Practice Guidelines for Management of Pain, Agitation and Delirium.

- ICU Liberation Collaborative
  - www.iculiberation.org



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B	Both SAT and SBT
C	Choice of Analgesia and Sedation
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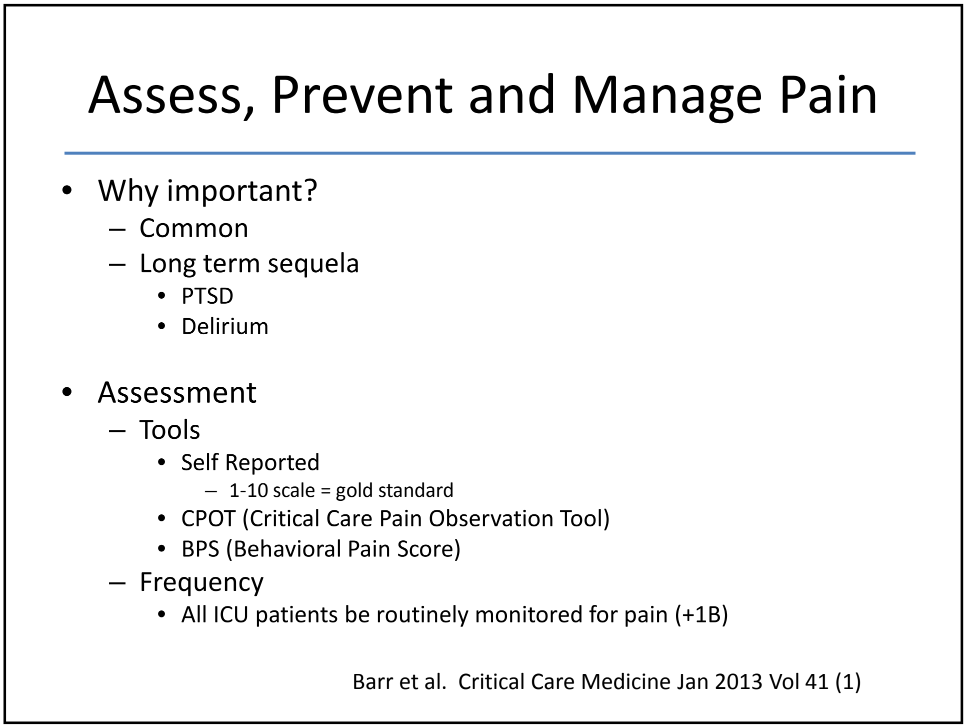

Assess, Prevent and Manage Pain

- Why important?
  - Common
  - Long term sequela
    - PTSD
    - Delirium

- Assessment
  - Tools
    - Self Reported
      - 1-10 scale = gold standard
    - CPOT (Critical Care Pain Observation Tool)
    - BPS (Behavioral Pain Score)
  - Frequency
    - All ICU patients be routinely monitored for pain (+1B)

Barr et al. Critical Care Medicine Jan 2013 Vol 41 (1)

ICU Care is Associated with Pain

Procedure	N (%)	Pre-procedural Pain Intensity	During Procedure Pain Intensity	Difference Median	p value
Chest tube removal	292 (6.1)	2 (0-4)	5 (3-7)	2.5 (0.5-4)	<0.0001
Wound drain removal	75 (1.6)	2 (0-4)	4.5 (2-7)	2 (0-4.5)	<0.0001
A line	199 (4.1)	1 (0-2.5)	4 (2-6)	2.75 (0-5)	<0.0001
ETT suctioning	767 (15.9)	1 (0-4)	4 (1-6)	1.5 (0.4)	<0.0001
Tracheal suctioning	302 (6.3)	1 (0-3.5)	4 (1-6)	1 (0-4)	<0.0001
Peripheral IV	315 (6.5)	1 (0-3)	3 (1-5.5)	1 (0-3)	<0.0001
Peripheral blood draw	328 (6.8)	0.5 (0-3)	3 (1-5)	1 (0-3)	<0.0001
Turning	873 (18.1)	1.75 (0-4)	3 (0.25-6)	1 (0-2.5)	<0.0001
Respiratory exercises	439 (9.1)	2 (0-4)	3 (1-5)	1 (0-2)	<0.0001
Positioning	371 (7.7)	1 (0-4)	3 (0-5)	1 (0-2)	<0.0001
Wound care	301 (6.3)	2 (0-4)	3 (1-6)	0.5 (0-2)	<0.0001
Mobilization	526 (10.9)	1 (0-3)	2 (0-5)	0 (0-2)	<0.0001

Puntillo et al. Am J Respir Crit Care Med. 2014 Vol 189 (1)

Treatment of Pain – PAD guidelines

- We recommend
  - Preemptive analgesics and or nonpharmacologic interventions prior to chest tube removal (strong recommendation, low quality of evidence).
  - Intravenous (IV) opioids be be considered the first line drug class of choice for non-neuropathic pain (strong recommendation, low quality of evidence).
  - Non opioid analgesics be considered to decrease the amount of opioids administered (weak recommendation, low quality of evidence)
  - Enterally administered gabapentin or carbamazepine in addition to IV opioids be considered for treatment of neuropathic pain.

Barr et al. Critical Care Medicine Jan 2013 Vol 41 (1)

A	Assess, Prevent & Manage Pain
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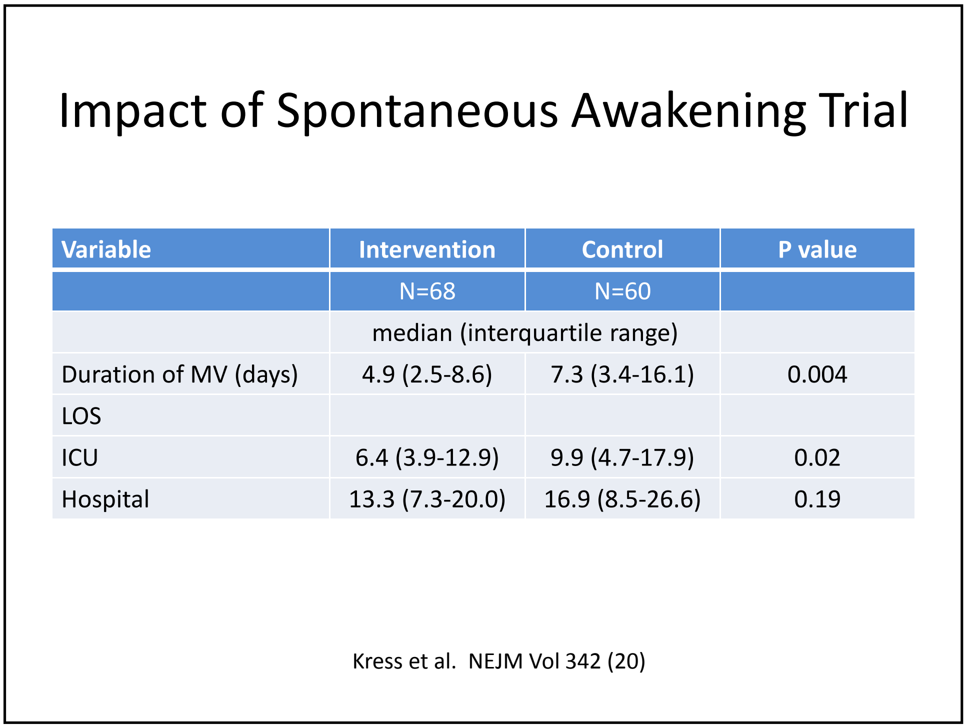
SAT (Spontaneous Awakening Trial)

- Stop continuous IV sedatives
- Stop continuous IV narcotics (unless needed for pain control)
- Restart ½ dose

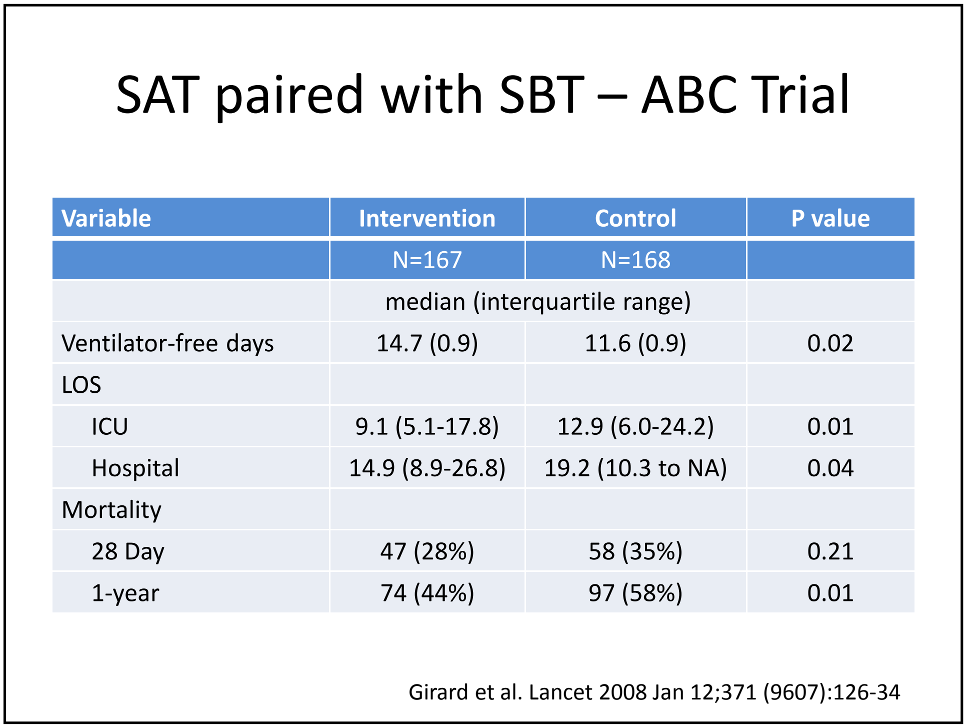
- Sedation minimization strategy



Impact of Spontaneous Awakening Trial

Variable	Intervention	Control	P value
	N=68	N=60	
	median (interquartile range)		
Duration of MV (days)	4.9 (2.5-8.6)	7.3 (3.4-16.1)	0.004
LOS			
ICU	6.4 (3.9-12.9)	9.9 (4.7-17.9)	0.02
Hospital	13.3 (7.3-20.0)	16.9 (8.5-26.6)	0.19

Kress et al. NEJM Vol 342 (20)



SAT paired with SBT – ABC Trial

Variable	Intervention	Control	P value
	N=167	N=168	
	median (interquartile range)		
Ventilator-free days	14.7 (0.9)	11.6 (0.9)	0.02
LOS			
ICU	9.1 (5.1-17.8)	12.9 (6.0-24.2)	0.01
Hospital	14.9 (8.9-26.8)	19.2 (10.3 to NA)	0.04
Mortality			
28 Day	47 (28%)	58 (35%)	0.21
1-year	74 (44%)	97 (58%)	0.01

Girard et al. Lancet 2008 Jan 12;371 (9607):126-34

A	Assess, Prevent & Manage Pain
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Choice of Analgesia and Sedation

- Reduced sedation improves patient outcomes.
- Implement strategies to minimize sedation
  - SAT
  - Goal directed sedation management
- Measure extent of sedation
  - RASS (Richmond Agitation and Sedation Scale)
  - Riker Sedation-Agitation Scale
- Choice of sedation
  - We suggest that sedation using nonbenzodiazepine sedatives may be preferred over benzodiazepines (weak recommendation, moderate quality of evidence)

Barr et al. Critical Care Medicine Jan 2013 Vol 41 (1)

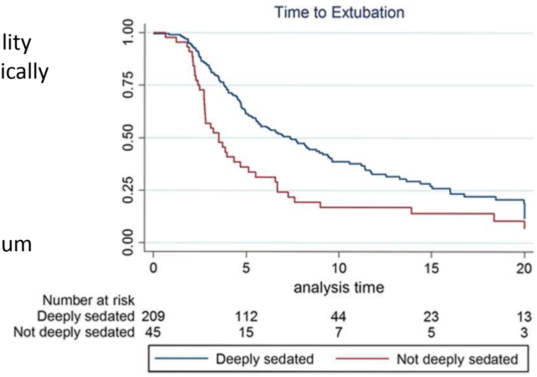
Oversedation – Poor Outcomes

Sedation and long term mortality
In mechanically ventilated critically
Ill adults.

N-259
Multicenter, longitudinal

Every 4 hrs sedation and delirium
Assessment

Early = First 48 hrs
Deep sedation <=3 RASS



Shehabi et al. Intensive Care Med (2013) 39:910–918

Oversedation – Poor Outcomes

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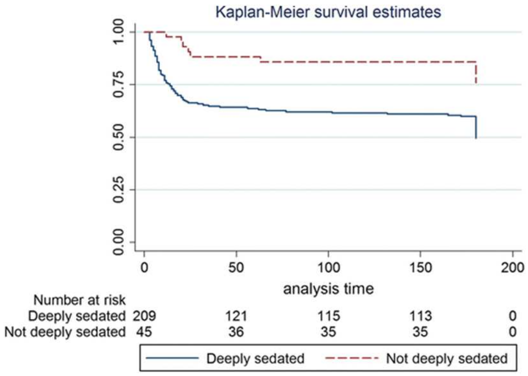
Deep sedation <=3 RASS



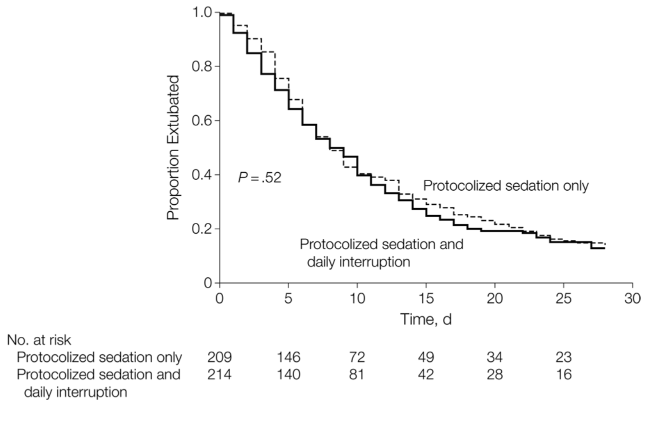
Shehabi et al. Intensive Care Med (2013) 39:910–918

SLEAP Trial

- SLEAP – Sedation Lightening and Evaluation of a Protocol
- Study design:
  - Protocolized sedation vs
  - Protocolized sedation with SAT
- n=430
- 16 tertiary care medical and surgical ICU
- Outcomes:
  - Primary
    - Time to extubation
  - Secondary
    - Duration
    - Sedation and opioid dose
    - Unintentional device removal

JAMA. 2012;308(19):1985-1992. doi:10.1001/jama.2012.13872

Mechanical Ventilation Duration
Protocolized Sedation vs SAT



JAMA. 2012;308(19):1985-1992. doi:10.1001/jama.2012.13872

A	Assess, Prevent & Manage Pain
B	Both SAT and SBT
C	Choice of Analgesia and Sedation
D	Delirium – Assess, Prevent & Manage
E	Early Mobility
F	Family Engagement

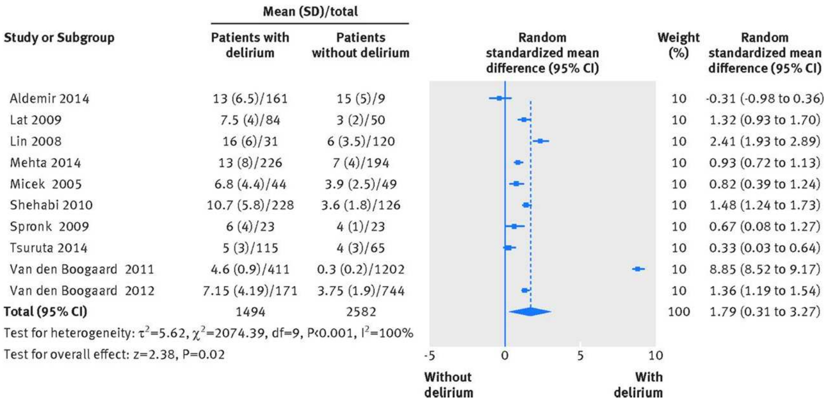
Delirium

- Syndrome of acute brain dysfunction characterized by inattention, fluctuating mental status, altered level of consciousness or disorganized thinking

Delirium

- Common
  - 81% of MV Patients
    - Ely et al. JAMA 2004;291:1753-1762
- Impact
  - Increased
    - Mechanical ventilation
    - ICU LOS
    - Hospital LOS
    - Cost
    - Post – ICU Cognitive impairment
    - Mortality –
      - Strongly associated with increased mortality even when adjusted for severity of disease

Delirium – Impact on MV Duration



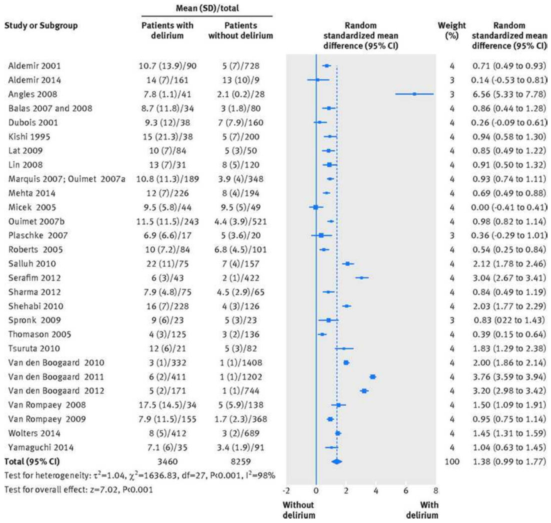
Study or Subgroup	Mean (SD)/total: Patients with delirium	Mean (SD)/total: Patients without delirium	Weight (%)	Random standardized mean difference (95% CI)
Aldemir 2014	13 (6.5)/161	15 (5)/9	10	-0.31 (-0.98 to 0.36)
Lat 2009	7.5 (4)/84	3 (2)/50	10	1.32 (0.93 to 1.70)
Lin 2008	16 (6)/31	6 (3.5)/120	10	2.41 (1.93 to 2.89)
Mehta 2014	13 (8)/226	7 (4)/194	10	0.93 (0.72 to 1.13)
Micek 2005	6.8 (4.4)/44	3.9 (2.5)/49	10	0.82 (0.39 to 1.24)
Shehabi 2010	10.7 (5.8)/228	3.6 (1.8)/126	10	1.48 (1.24 to 1.73)
Spronk 2009	6 (4)/23	4 (1)/23	10	0.67 (0.08 to 1.27)
Tsuruta 2014	5 (3)/115	4 (3)/65	10	0.33 (0.03 to 0.64)
Van den Boogaard 2011	4.6 (0.9)/411	0.3 (0.2)/1202	10	8.85 (8.52 to 9.17)
Van den Boogaard 2012	7.15 (4.19)/171	3.75 (1.9)/744	10	1.36 (1.19 to 1.54)
Total (95% CI)	1494	2582	100	1.79 (0.31 to 3.27)

Test for heterogeneity: $\tau^2=5.62$, $\chi^2=2074.39$, df=9, $P<0.001$, $I^2=100\%$

Test for overall effect: z=2.38, P=0.02

Jorge I F Salluh et al. BMJ 2015;350:bmj.h2538

Delirium – Impact on ICU LOS



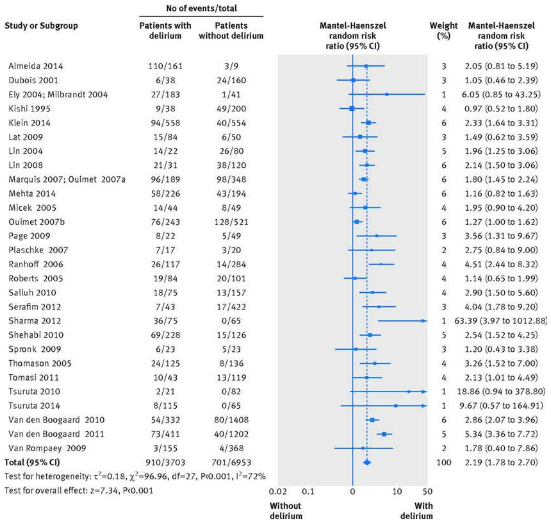
Study or Subgroup	Mean (SD)/total: Patients with delirium	Mean (SD)/total: Patients without delirium	Weight (%)	Random standardized mean difference (95% CI)
Aldemir 2001	10.7 (13.9)/90	5 (7)/728	4	0.71 (0.49 to 0.93)
Aldemir 2014	14 (7)/161	13 (10)/9	3	0.14 (-0.53 to 0.81)
Angles 2008	7.8 (1.1)/41	2.1 (0.2)/28	3	6.56 (5.33 to 7.78)
Balas 2007 and 2008	8.7 (11.8)/34	3 (1.8)/80	4	0.86 (0.44 to 1.28)
Dubois 2001	9.3 (12)/38	7 (7.9)/160	4	0.26 (-0.09 to 0.61)
Kishi 1995	15 (21.3)/38	5 (7)/200	4	0.94 (0.58 to 1.30)
Lat 2009	10 (7)/84	5 (3)/50	4	0.85 (0.49 to 1.22)
Lin 2008	13 (7)/31	8 (5)/120	4	0.91 (0.50 to 1.32)
Marquis 2007; Ouimet 2007a	10.8 (11.3)/189	3.9 (4)/348	4	0.93 (0.74 to 1.11)
Mehta 2014	12 (7)/226	8 (4)/194	4	0.69 (0.49 to 0.88)
Micek 2005	9.5 (5.8)/44	9.5 (5)/49	4	0.00 (-0.41 to 0.41)
Ouimet 2007b	11.5 (11.5)/243	4.4 (3.9)/521	4	0.98 (0.82 to 1.14)
Plaschke 2007	6.9 (6.6)/17	5 (3.6)/20	3	0.36 (-0.29 to 1.01)
Roberts 2005	10 (7.2)/84	6.8 (4.5)/101	4	0.54 (0.25 to 0.84)
Salluh 2010	22 (11)/75	7 (4)/157	4	2.12 (1.78 to 2.46)
Serafim 2012	6 (3)/43	2 (1)/422	4	3.04 (2.67 to 3.41)
Sharma 2012	7.9 (4.8)/75	4.5 (2.9)/65	4	0.84 (0.49 to 1.19)
Shehabi 2010	16 (7)/228	4 (3)/126	4	2.03 (1.77 to 2.29)
Spronk 2009	9 (6)/23	5 (3)/23	3	0.83 (022 to 1.43)
Thomason 2005	4 (3)/125	3 (2)/136	4	0.39 (0.15 to 0.64)
Tsuruta 2010	12 (6)/21	5 (3)/82	4	1.83 (1.29 to 2.38)
Van den Boogaard 2010	3 (1)/332	1 (1)/1408	4	2.00 (1.86 to 2.14)
Van den Boogaard 2011	6 (2)/411	1 (1)/1202	4	3.76 (3.59 to 3.94)
Van den Boogaard 2012	5 (2)/171	1 (1)/744	4	3.20 (2.98 to 3.42)
Van Rompaey 2008	17.5 (14.5)/34	5 (5.9)/138	4	1.50 (1.09 to 1.91)
Van Rompaey 2009	7.9 (11.5)/155	1.7 (2.3)/368	4	0.95 (0.75 to 1.14)
Wolters 2014	8 (5)/412	3 (2)/689	4	1.45 (1.31 to 1.59)
Yamaguchi 2014	7.1 (6)/35	3.4 (1.9)/91	4	1.04 (0.63 to 1.45)
Total (95% CI)	3460	8259	100	1.38 (0.99 to 1.77)

Test for heterogeneity: $\tau^2=1.04$, $\chi^2=1636.83$, df=27, P<0.001, $I^2=98\%$

Test for overall effect: z=7.02, P<0.001

Jorge I F Salluh et al. BMJ 2015;350:bmj.h2538

Delirium – Impact on Hospital Mortality



Study or Subgroup	No of events/total: Patients with delirium	No of events/total: Patients without delirium	Weight (%)	Mantel-Haenszel random risk ratio (95% CI)
Almeida 2014	110/161	3/9	3	2.05 (0.81 to 5.19)
Dubois 2001	6/38	24/160	3	1.05 (0.46 to 2.39)
Ely 2004; Milbrandt 2004	27/183	1/41	1	6.05 (0.85 to 43.25)
Kishi 1995	9/38	49/200	4	0.97 (0.52 to 1.80)
Klein 2014	94/558	40/554	6	2.33 (1.64 to 3.31)
Lat 2009	15/84	6/50	3	1.49 (0.62 to 3.59)
Lin 2004	14/22	26/80	5	1.96 (1.25 to 3.06)
Lin 2008	21/31	38/120	6	2.14 (1.50 to 3.06)
Marquis 2007; Ouimet 2007a	96/189	98/348	6	1.80 (1.45 to 2.24)
Mehta 2014	58/226	43/194	6	1.16 (0.82 to 1.63)
Micek 2005	14/44	8/49	4	1.95 (0.90 to 4.20)
Ouimet 2007b	76/243	128/521	6	1.27 (1.00 to 1.62)
Page 2009	8/22	5/49	3	3.56 (1.31 to 9.67)
Plaschke 2007	7/17	3/20	2	2.75 (0.84 to 9.00)
Ranhoff 2006	26/117	14/284	4	4.51 (2.44 to 8.32)
Roberts 2005	19/84	20/101	4	1.14 (0.65 to 1.99)
Salluh 2010	18/75	13/157	4	2.90 (1.50 to 5.60)
Serafim 2012	7/43	17/422	3	4.04 (1.78 to 9.20)
Sharma 2012	36/75	0/65	1	63.39 (3.97 to 1012.88)
Shehabi 2010	69/228	15/126	5	2.54 (1.52 to 4.25)
Spronk 2009	6/23	5/23	3	1.20 (0.43 to 3.38)
Thomason 2005	24/125	8/136	4	3.26 (1.52 to 7.00)
Tomasi 2011	10/43	13/119	4	2.13 (1.01 to 4.49)
Tsuruta 2010	2/21	0/82	1	18.86 (0.94 to 378.80)
Tsuruta 2014	8/115	0/65	1	9.67 (0.57 to 164.91)
Van den Boogaard 2010	54/332	80/1408	6	2.86 (2.07 to 3.96)
Van den Boogaard 2011	73/411	40/1202	5	5.34 (3.36 to 7.72)
Van Rompaey 2009	3/155	4/368	2	1.78 (0.40 to 7.86)
Total (95% CI)	910/3703	701/6953	100	2.19 (1.78 to 2.70)

Test for heterogeneity: $\tau^2=0.18$, $\chi^2=96.96$, df=27, P<0.001, $I^2=72\%$

Test for overall effect: z=7.34, P<0.001

Jorge I F Salluh et al. BMJ 2015;350:bmj.h2538

Assessment of Delirium

- Most commonly used scales
  - Confusion Assessment Method – ICU
  - Intensive Care Delirium Screening Checklist

Delirium *Prevention*– PAD Guidelines

- Recommend early mobilization (strong recommendation, moderate quality of evidence)
- No recommendation for a pharmacologic delirium prevention protocol (low quality of evidence)
- No recommendation for using a combined non-pharmacologic and pharmacologic delirium prevention protocol (no data, low quality of evidence).
- Do not suggest that either haloperidol or atypical antipsychotics be administered to prevent delirium (weak recommendation, low quality of evidence)

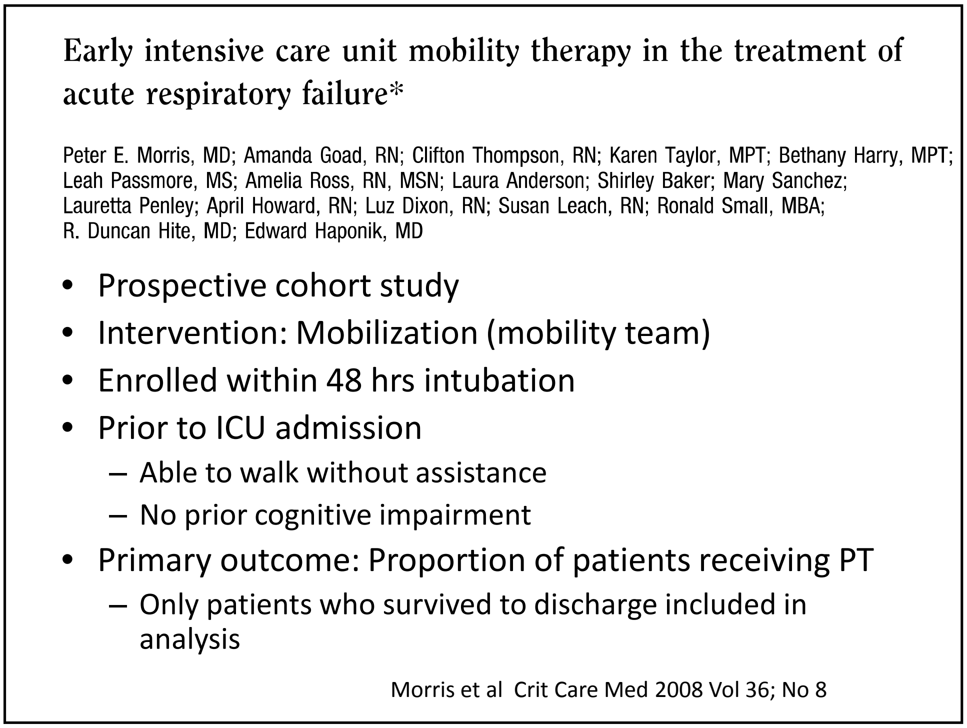
Barr et al. Critical Care Medicine Jan 2013 Vol 41 (1)

Delirium *Treatment* – PAD Guidelines

- No evidence that treatment with haloperidol reduces duration of delirium (no evidence)
- Atypical antipsychotics may reduce duration of delirium (low quality of evidence)
- In adult ICU patients with delirium unrelated to EtOH or benzodiazepine withdrawal, continuous infusion of dexmedetomidine rather than benzodiazepines be used to reduce duration of delirium (weak recommendation, moderate quality of evidence)

Barr et al. Critical Care Medicine Jan 2013 Vol 41 (1)

A	Assess, Prevent & Manage Pain
B	Both SAT and SBT
C	Choice of Analgesia and Sedation
D	Delirium – Assess, Prevent & Manage
E	Early Mobility
F	Family Engagement

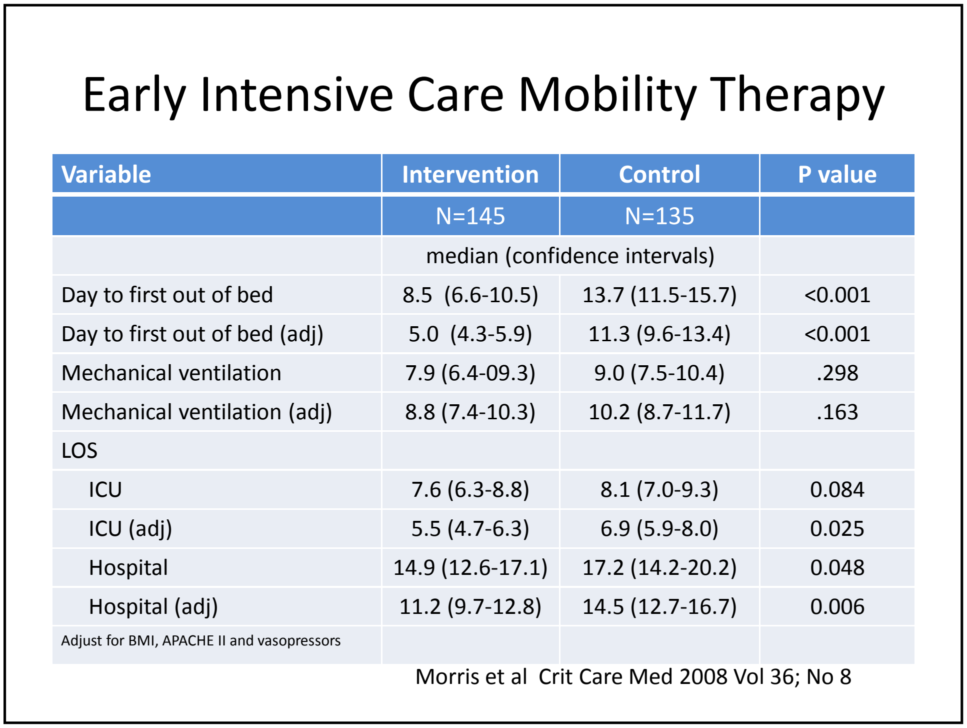


Early intensive care unit mobility therapy in the treatment of acute respiratory failure*

Peter E. Morris, MD; Amanda Goad, RN; Clifton Thompson, RN; Karen Taylor, MPT; Bethany Harry, MPT;
Leah Passmore, MS; Amelia Ross, RN, MSN; Laura Anderson; Shirley Baker; Mary Sanchez;
Lauretta Penley; April Howard, RN; Luz Dixon, RN; Susan Leach, RN; Ronald Small, MBA;
R. Duncan Hite, MD; Edward Haponik, MD

- Prospective cohort study
- Intervention: Mobilization (mobility team)
- Enrolled within 48 hrs intubation
- Prior to ICU admission
  - Able to walk without assistance
  - No prior cognitive impairment
- Primary outcome: Proportion of patients receiving PT
  - Only patients who survived to discharge included in analysis

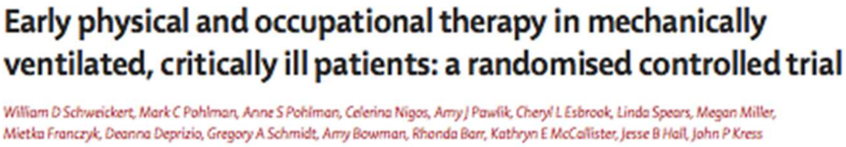
Morris et al Crit Care Med 2008 Vol 36; No 8



Early Intensive Care Mobility Therapy

Variable	Intervention	Control	P value
	N=145	N=135	
	median (confidence intervals)		
Day to first out of bed	8.5 (6.6-10.5)	13.7 (11.5-15.7)	<0.001
Day to first out of bed (adj)	5.0 (4.3-5.9)	11.3 (9.6-13.4)	<0.001
Mechanical ventilation	7.9 (6.4-09.3)	9.0 (7.5-10.4)	.298
Mechanical ventilation (adj)	8.8 (7.4-10.3)	10.2 (8.7-11.7)	.163
LOS			
ICU	7.6 (6.3-8.8)	8.1 (7.0-9.3)	0.084
ICU (adj)	5.5 (4.7-6.3)	6.9 (5.9-8.0)	0.025
Hospital	14.9 (12.6-17.1)	17.2 (14.2-20.2)	0.048
Hospital (adj)	11.2 (9.7-12.8)	14.5 (12.7-16.7)	0.006
Adjust for BMI, APACHE II and vasopressors			

Morris et al Crit Care Med 2008 Vol 36; No 8



Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial

William D Schweickert, Mark C Pohlman, Anne S Pohlman, Celerina Nigos, Amy J Pawlik, Cheryl L Esbrook, Linda Spears, Megan Miller, Mietka Franczyk, Deanna Deprizio, Gregory A Schmidt, Amy Bowman, Rhonda Barr, Kathryn E McCallister, Jesse B Hall, John P Kress

- Intervention: Early physical exercise and mobilization (PT and OT) *paired* with SAT
- Control: SAT (and usual care)
- Inclusion criteria
  - > 18 years of age
  - MV < 72 hrs
  - Baseline functional independence
- 104 patients

Schweickert et al Lancet 2009 Vol 373

Impact of Early Mobilization

	Intervention	Control	p value
	(n=49)	(n=55)	
Return to independent functional status	29 (59%)	19 (35%)	0.02
ICU Delirium (days)	2.0 (0.0-6.0)	4.0 (2.0-7.0)	0.03
ICU acquired paresis at hospital discharge	15 (31%)	27 (49%)	0.09
Ventilator free days	23.5 (7.4-25.6)	21.1 (0.0-23.8)	0.05
ICU LOS	5.9 (4.5-13.2)	7.9 (6.1-12.9)	0.08
Hospital LOS	13.5 (8.0-23.1)	12.9 (8.9-19.8)	0.93
Hospital Mortality	9 (18%)	14 (25%)	0.53

Schweickert et al Lancet 2009 Vol 373

Benefits of early mobilization

- Reduced delirium
- Reduced mechanical ventilation days
- Reduced ICU LOS
- Reduced Hospital LOS

A	Assess, Prevent & Manage Pain
B	Both SAT and SBT
C	Choice of Analgesia and Sedation
D	Delirium – Assess, Prevent & Manage
E	Early Mobility
F	Family Engagement

Impact on Family Members

- Post traumatic stress symptoms 33.1%
- Subgroups
  - Felt information was incomplete (48.4%)
  - Relative died in ICU (50%)
  - Relative died after end-of-life decisions (60%)
  - Shared in EOL decision making (81.8%)

Azoulay et al. Am J Respir Crit Care Med Vol 171. pp 987–994, 2005

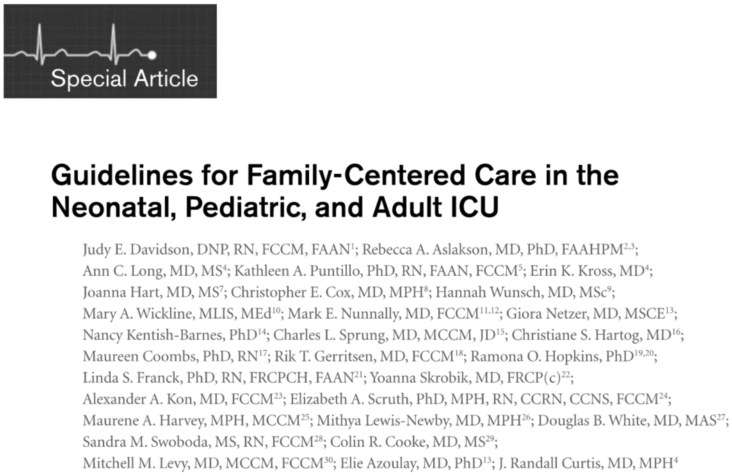
Post Intensive Care Syndrome - Family

- Acute stress disorder
  - 33% of parents with children in ICU
- Posttraumatic stress disorder (PTSD)
  - Median 21%; range 13-56%
- Anxiety
  - Median 40%; range 21-56%
- Depression
  - Median 23%; range 8-42%

Davidson et al. Crit Care Med 2012 Vol. 40, No. 2

Family Engagement - Interventions

- Communication via structured family meetings
- Family presence / participation
  - Open visitation policies
  - Family involvement on rounds
  - Family presence at codes / procedures
- Role of ethics or palliative care consultation



Special Article

Guidelines for Family-Centered Care in the Neonatal, Pediatric, and Adult ICU

Judy E. Davidson, DNP, RN, FCCM, FAAN[1]; Rebecca A. Aslakson, MD, PhD, FAAHPM[2,3];
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Nancy Kentish-Barnes, PhD[14]; Charles L. Sprung, MD, MCCM, JD[15]; Christiane S. Hartog, MD[16];
Maureen Coombs, PhD, RN[17]; Rik T. Gerritsen, MD, FCCM[18]; Ramona O. Hopkins, PhD[19,20];
Linda S. Franck, PhD, RN, FRCPCH, FAAN[21]; Yoanna Skrobik, MD, FRCP(c)[22];
Alexander A. Kon, MD, FCCM[23]; Elizabeth A. Scruth, PhD, MPH, RN, CCRN, CCNS, FCCM[24];
Maurene A. Harvey, MPH, MCCM[25]; Mithya Lewis-Newby, MD, MPH[26]; Douglas B. White, MD, MAS[27];
Sandra M. Swoboda, MS, RN, FCCM[28]; Colin R. Cooke, MD, MS[29];
Mitchell M. Levy, MD, MCCM, FCCM[30]; Elie Azoulay, MD, PhD[13]; J. Randall Curtis, MD, MPH[4]

Critical Care Medicine: January 2017 - Volume 45 - Issue 1 - p 103–128

Impact of the Bundle

Improving Hospital Survival and Reducing Brain Dysfunction at Seven California Community Hospitals: Implementing PAD Guidelines Via the ABCDEF Bundle in 6,064 Patients*

Mary Ann Barnes-Daly, MS, RN, CCRN, DC[1]; Gary Phillips, MAS[2]; E. Wesley Ely, MD, MPH, FCCM[3,4]

- Aim: Association between bundle compliance and outcomes
  - Hospital survival
  - Delirium or coma free days
- Prospective cohort; ICU patients
- 7 community hospitals
  - Mechanical ventilation (MV) and non MV
- Utilized earlier ABCDEF definition (same processes / reorganized)

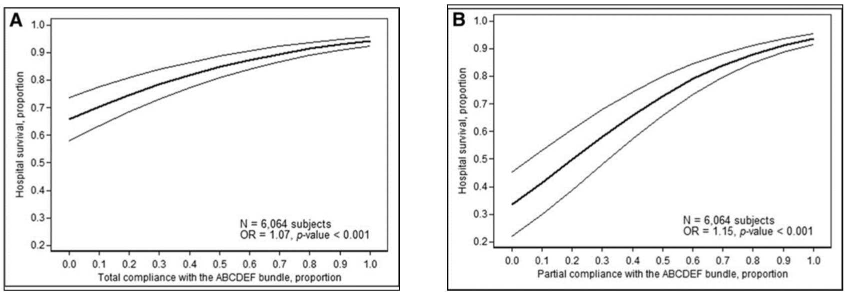
Barnes-Daly et al. Critical Care Medicine. 45(2):171-178, February 2017.

Metrics – Implementing PAD via ABCDEF

Process		Metric required (over past 24 hrs)
A	Awakening (SAT)	Turn off all sedation
B	Breathing (SBT)	CPAP PSV 5/5 or "blow-by" for 30 mins
C1	Coordination of A&B	RN and RRT confirm at rounds
C2	Choice of drugs	Pharmacist attestation at rounds that PAD was being followed
D	Delirium	CAM-ICU used to document
E	Early mobility	Patient had been maximally mobilized
F	Family engagement	Patient / family had participated in rounds or family conference held

Barnes-Daly et al. Critical Care Medicine. 45(2):171-178, February 2017.

Results – Impact on Hospital Survival



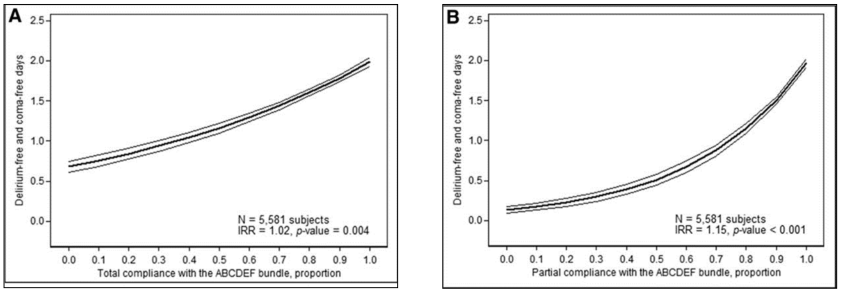
Total Compliance

Partial Compliance

Adjusted for patient age, APACHE III, and the proportion of days a patient was mechanically ventilated

Barnes-Daly et al. Critical Care Medicine. 45(2):171-178, February 2017.

Results – Delirium / Coma Free Days



Total Compliance

Partial Compliance

Adjusted for patient age, APACHE III, and the proportion of days a patient was mechanically ventilated

Barnes-Daly et al. Critical Care Medicine. 45(2):171-178, February 2017.

Summary

- Use of the bundle can improve patient care.
  - – Short term
  - – Long term
    - Aim to reduce Post ICU Syndrome
      - – Patient and Family
- ABCDEF Bundle support the PAD Guidelines of the SCCM
- ABCDEF bundle can be successfully as a research protocol but also as a QI initiative in any hospital
  - – Interprofessional team

Question 1

An 80 y.o. male with history of COPD is admitted to ICU with pneumonia and hypoxemic respiratory failure. Mechanical ventilation is initiated and he is started on continuous IV midazolam for sedation. Which of the following interventions is not indicated to minimize the risk of delirium?

a) Daily spontaneous awakening trial (SAT).
b) Midazolam order titrated to RASS 0 to -1
c) Initiation of haloperidol delirium prevention protocol.
d) Mobilization at the earliest time possible.

Question 1 - Answer

Which of the following interventions is not indicated to minimize the risk of delirium?

a) Daily spontaneous awakening trial (SAT).
b) Benzodiazepines titrated to RASS 0 to -1
c) Initiation of haloperidol prevention protocol.
d) Mobilization at the earliest time possible.

Daily interruption of sedation and goal targeted sedation titration are two well established strategies to minimize total sedation dose. Minimization of benzodiazepine dose is associated with reduced incidence of delirium. Early mobility studies have demonstrated reduced delirium rates. There is no evidence to support protocolized use of haloperidol to prevent delirium.

Question 2

An 65 y.o. female with stage IV non-small cell lung cancer is admitted to the ICU with a chemotherapy related pneumonitis and acute respiratory failure. At home she is on standing (and as needed oxycodone) to control pain from multiple rib and spine metastases. Mechanical ventilation is initiated. She is placed on continuous midazolam and fentanyl drip. Which of the following interventions would be most appropriate to minimize duration of mechanical ventilation?

a) Daily spontaneous awakening trial (SAT) with cessation of continuous IV midazolam and fentanyl.
b) Daily SAT with cessation of continuous IV midazolam and continuation of fentanyl to control any pain. When needed restart midazolam at prior dose.
c) Transition from midazolam and fentanyl to propofol
d) Assure that all sedation orders are written to titrate RASS to 0 to -1 and opiate to titrate to pain..

Question 2

Which of the following interventions is most appropriate to minimize duration of mechanical ventilation?

a) Daily spontaneous awakening trial (SAT) with cessation of continuous IV midazolam and fentanyl.

b) Daily SAT with cessation of continuous IV midazolam and continuation of fentanyl to control any pain. When needed restart midazolam at prior dose.

c) Transition from midazolam and fentanyl to propofol

d) Assure that all sedation orders are written to titrate RASS to 0 to -1 and opiate to titrate to pain.

Daily cessation of sedation is well established intervention to reduce mechanical ventilation days. In this case option A is not most appropriate since the patient is on chronic opiate at home and the SAT should be performed with continuation of continuous opiate to control baseline pain (equivalent to dose given at home). Option B directs restart of midazolam at prior dose and the continuous IV drip should be started at *half* the prior rate and then titrated. It is reasonable to consider transition from midazolam to propofol but the patient needs some opiate as pain must be addressed. Control of pain and titration of sedation to RASS 0 to -1 is the best answer.

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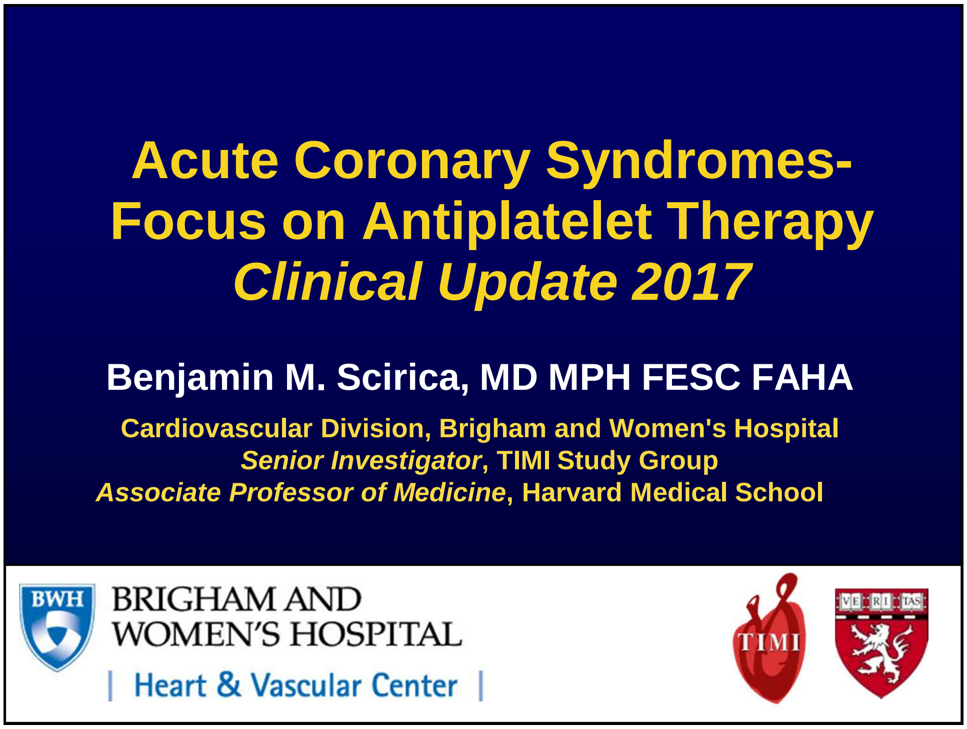

Acute Coronary Syndromes- Focus on Antiplatelet Therapy
Clinical Update 2017

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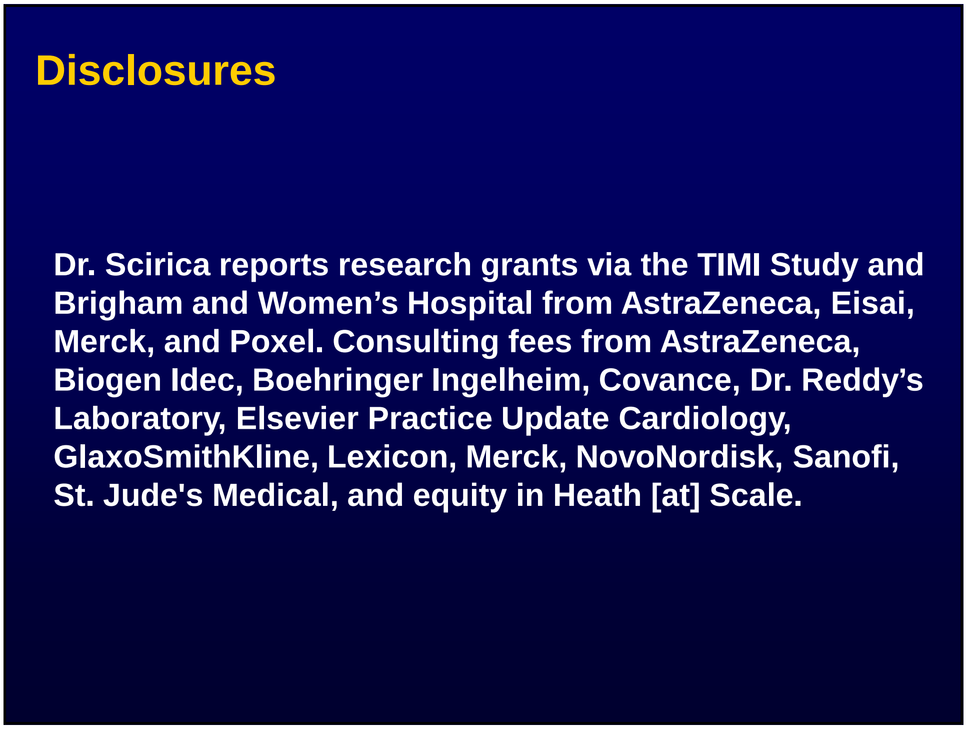
Associate Professor of Medicine, Harvard Medical School

BWH BRIGHAM AND WOMEN'S HOSPITAL
| Heart & Vascular Center |

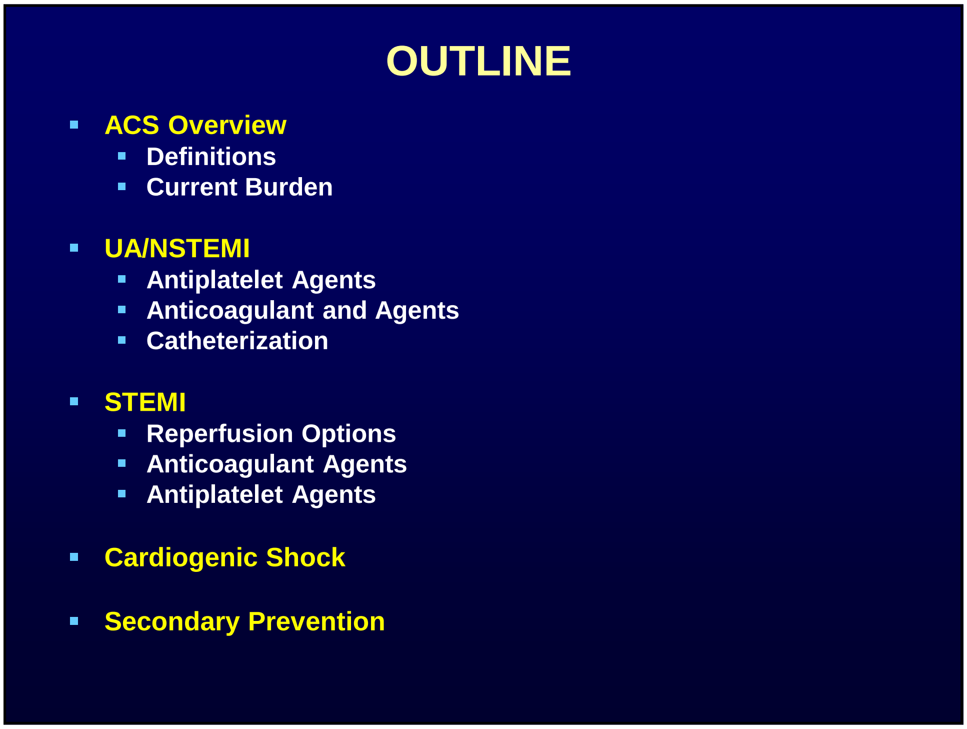
TIMI

VE RI TAS



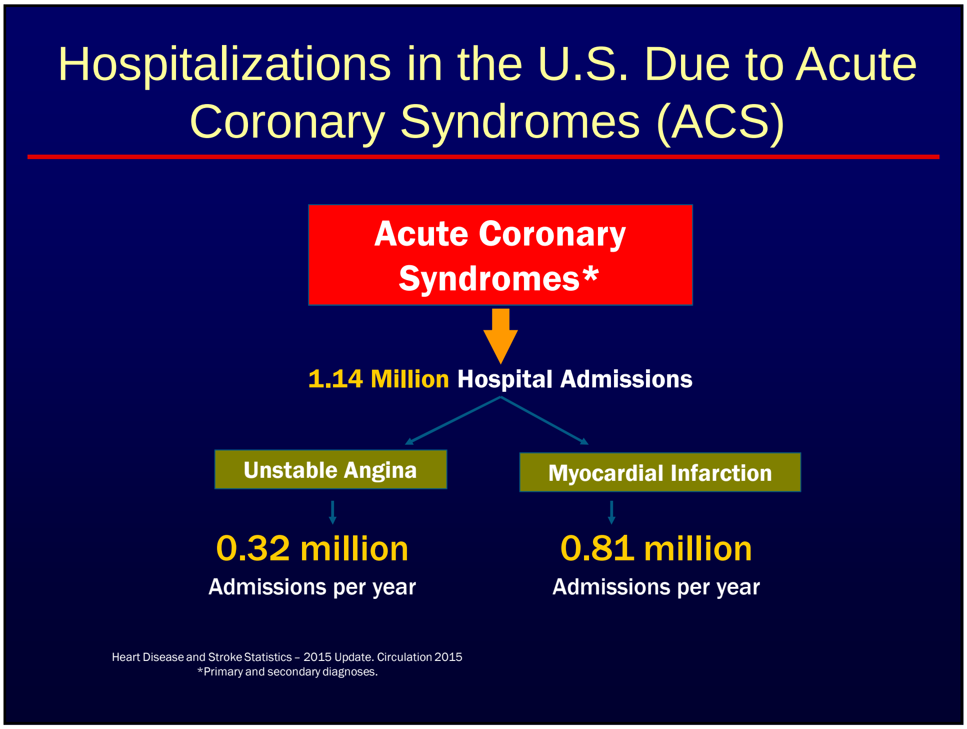
Disclosures

Dr. Scirica reports research grants via the TIMI Study and Brigham and Women's Hospital from AstraZeneca, Eisai, Merck, and Poxel. Consulting fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr. Reddy's Laboratory, Elsevier Practice Update Cardiology, GlaxoSmithKline, Lexicon, Merck, NovoNordisk, Sanofi, St. Jude's Medical, and equity in Heath [at] Scale.



OUTLINE

- ACS Overview
  - Definitions
  - Current Burden
- UA/NSTEMI
  - Antiplatelet Agents
  - Anticoagulant and Agents
  - Catheterization
- STEMI
  - Reperfusion Options
  - Anticoagulant Agents
  - Antiplatelet Agents
- Cardiogenic Shock
- Secondary Prevention



Hospitalizations in the U.S. Due to Acute Coronary Syndromes (ACS)

Acute Coronary Syndromes*

1.14 Million Hospital Admissions

Unstable Angina

0.32 million
Admissions per year

Myocardial Infarction

0.81 million
Admissions per year

Heart Disease and Stroke Statistics – 2015 Update. Circulation 2015
*Primary and secondary diagnoses.

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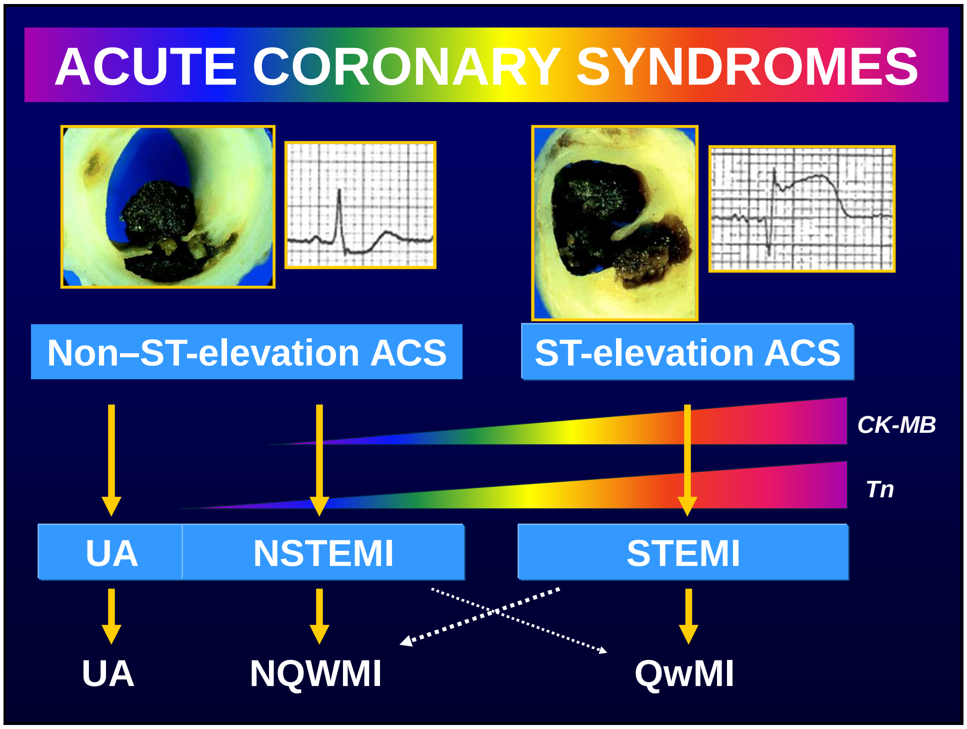


ACUTE CORONARY SYNDROMES

Non–ST-elevation ACS

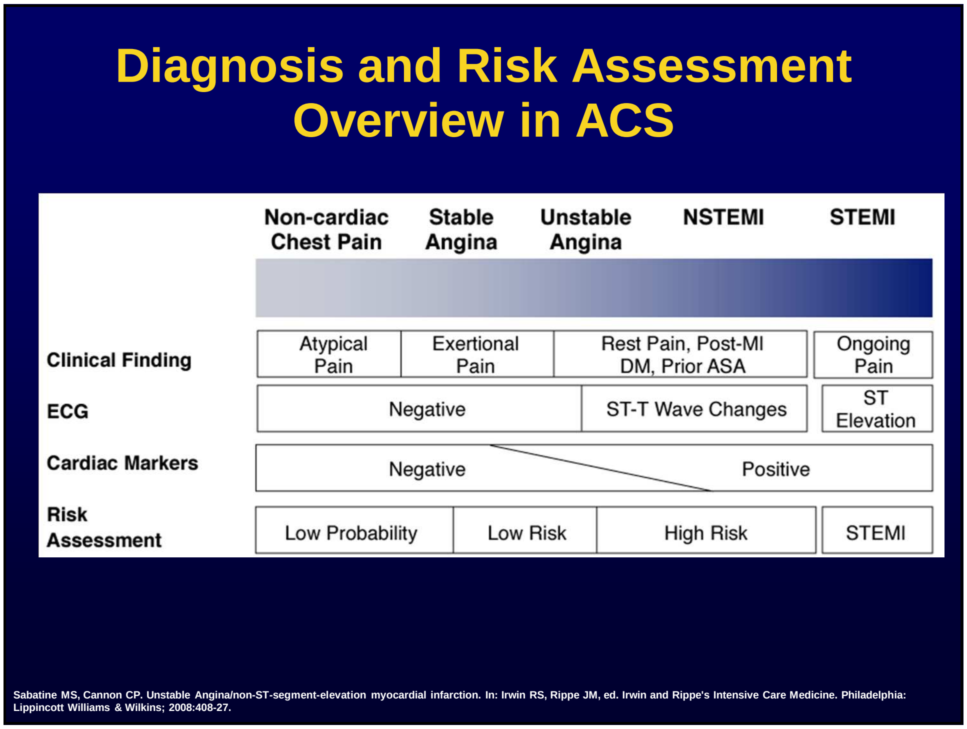
ST-elevation ACS

CK-MB

Tn

UA | NSTEMI | STEMI

UA | NQWMI | QwMI



Diagnosis and Risk Assessment Overview in ACS

	Non-cardiac Chest Pain	Stable Angina	Unstable Angina	NSTEMI	STEMI
Clinical Finding	Atypical Pain	Exertional Pain	Rest Pain, Post-MI DM, Prior ASA		Ongoing Pain
ECG	Negative		ST-T Wave Changes		ST Elevation
Cardiac Markers	Negative			Positive	
Risk Assessment	Low Probability	Low Risk	High Risk		STEMI

Sabatine MS, Cannon CP. Unstable Angina/non-ST-segment-elevation myocardial infarction. In: Irwin RS, Rippe JM, ed. Irwin and Rippe's Intensive Care Medicine. Philadelphia: Lippincott Williams & Wilkins; 2008:408-27.

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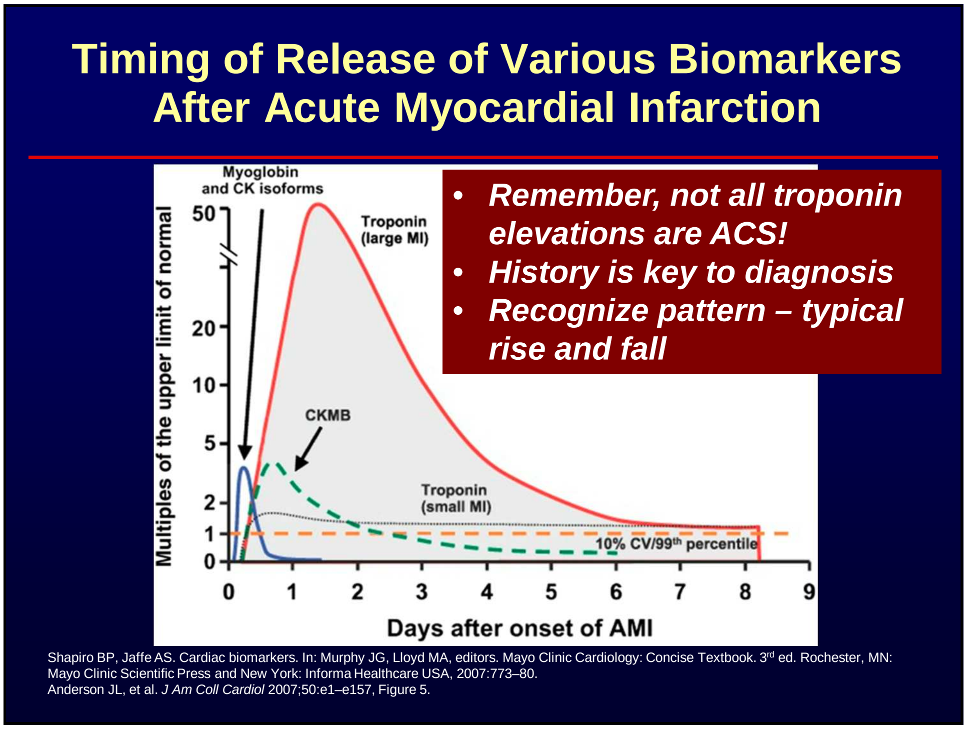
Universal Definitions of MI

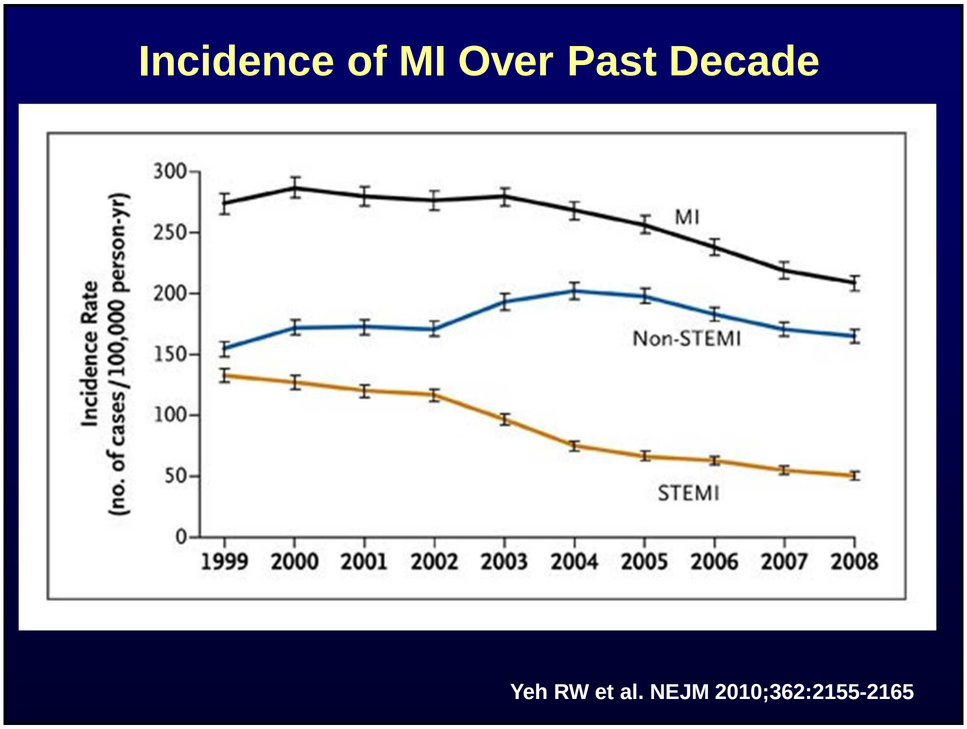
- Type 1: Spontaneous MI related to ischemia due to a primary coronary (eg. plaque erosion and/or rupture)
- Type 2: MI from ischemia due to either ↑ O2 demand or ↓ supply, e.g., spasm, embolism, anemia, arrhythmias, hypertension.
- Type 3: Sudden unexpected death likely from MI.
- Type 4a: MI associated with PCI.
- Type 4b: MI associated with stent thrombosis
- Type 5: MI associated with CABG.



Timing of Release of Various Biomarkers After Acute Myocardial Infarction

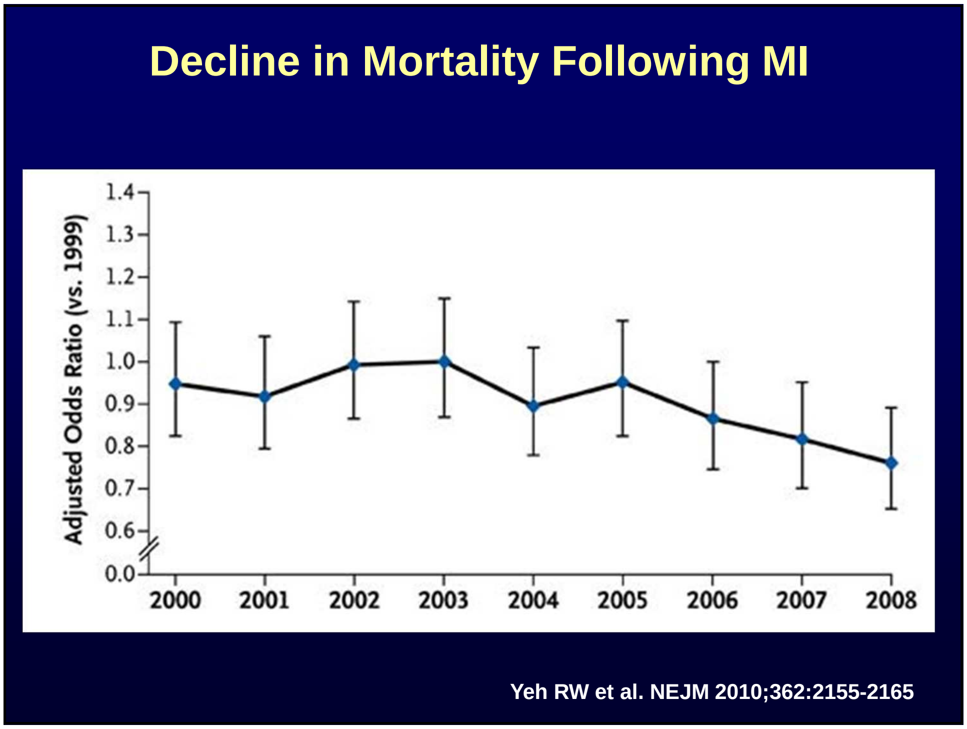
- ***Remember, not all troponin elevations are ACS!***
- ***History is key to diagnosis***
- ***Recognize pattern – typical rise and fall***

Shapiro BP, Jaffe AS. Cardiac biomarkers. In: Murphy JG, Lloyd MA, editors. Mayo Clinic Cardiology: Concise Textbook. 3rd ed. Rochester, MN: Mayo Clinic Scientific Press and New York: Informa Healthcare USA, 2007:773–80.
Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 5.



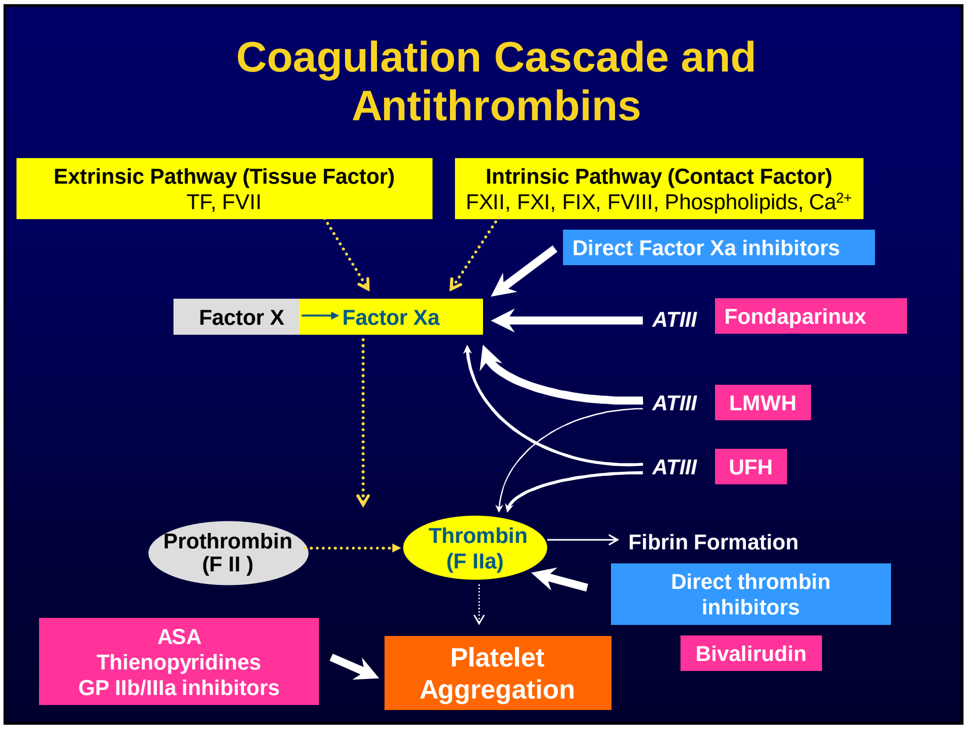
Incidence of MI Over Past Decade

Yeh RW et al. NEJM 2010;362:2155-2165



Decline in Mortality Following MI

Yeh RW et al. NEJM 2010;362:2155-2165



Coagulation Cascade and Antithrombins

Extrinsic Pathway (Tissue Factor)
TF, FVII

Intrinsic Pathway (Contact Factor)
FXII, FXI, FIX, FVIII, Phospholipids, Ca^{2+}

Direct Factor Xa inhibitors

Factor X → Factor Xa

ATIII Fondaparinux

ATIII LMWH

ATIII UFH

Prothrombin (F II)

Thrombin (F IIa)

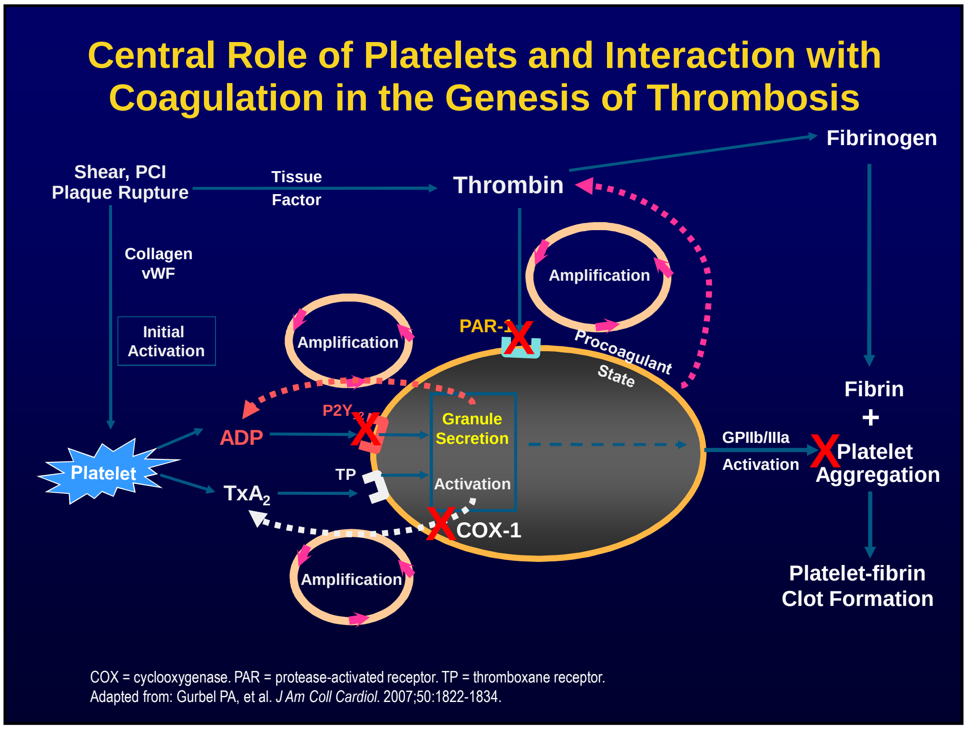
Fibrin Formation

Direct thrombin inhibitors

Bivalirudin

ASA
Thienopyridines
GP IIb/IIIa inhibitors

Platelet Aggregation



Central Role of Platelets and Interaction with Coagulation in the Genesis of Thrombosis

Shear, PCI
Plaque Rupture
Tissue Factor
Thrombin
Fibrinogen
Collagen
vWF
Initial Activation
Amplification
Amplification
PAR-1
Procoagulant State
Platelet
ADP
$P2Y_{12}$
Granule Secretion
TP
TxA_2
Activation
COX-1
Amplification
GPIIb/IIIa Activation
Fibrin
+
Platelet Aggregation
Platelet-fibrin Clot Formation

COX = cyclooxygenase. PAR = protease-activated receptor. TP = thromboxane receptor.
Adapted from: Gurbel PA, et al. *J Am Coll Cardiol.* 2007;50:1822-1834.

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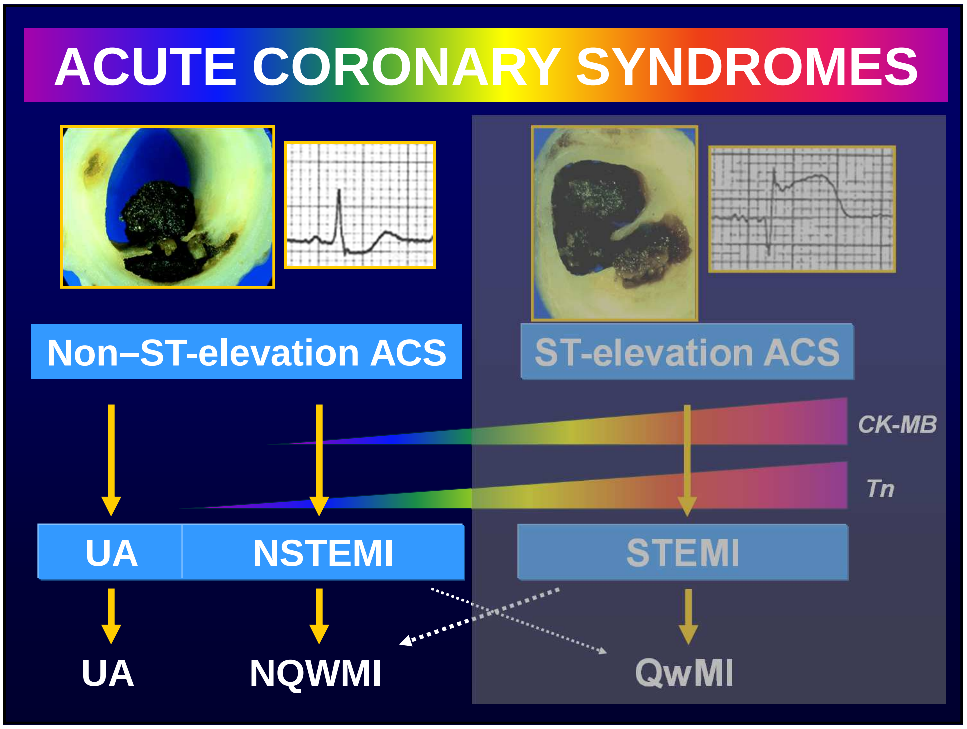
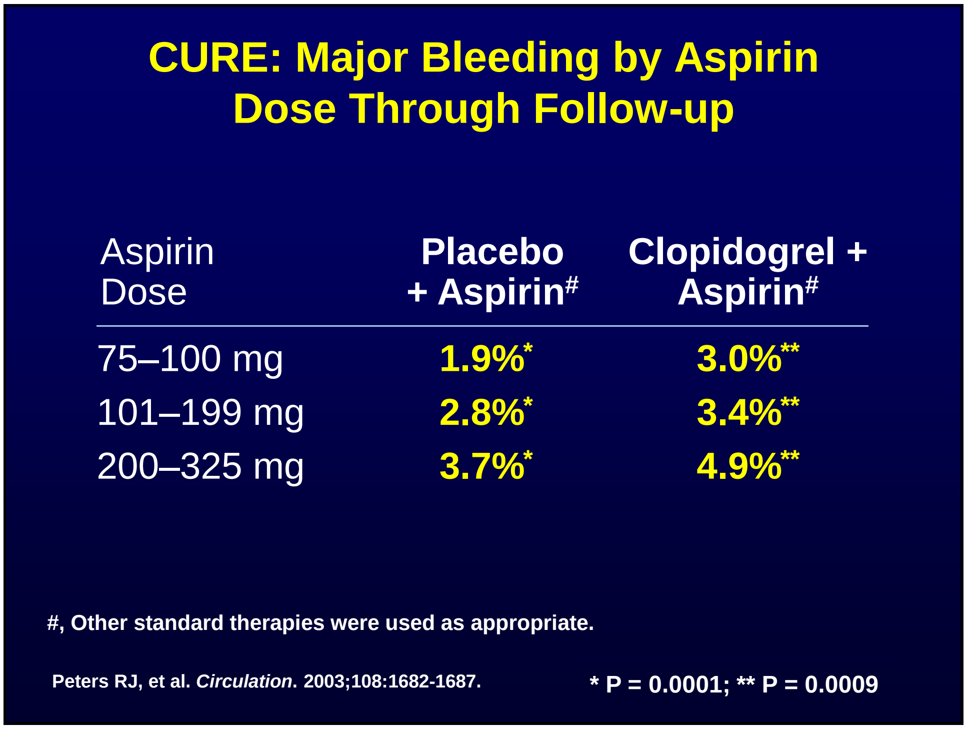


ACUTE CORONARY SYNDROMES

Non–ST-elevation ACS
ST-elevation ACS
CK-MB
Tn
UA
NSTEMI
STEMI
UA
NQWMI
QwMI



CURE: Major Bleeding by Aspirin Dose Through Follow-up

Aspirin Dose	Placebo + Aspirin#	Clopidogrel + Aspirin#
75–100 mg	1.9%*	3.0%**
101–199 mg	2.8%*	3.4%**
200–325 mg	3.7%*	4.9%**

#, Other standard therapies were used as appropriate.

Peters RJ, et al. *Circulation.* 2003;108:1682-1687.

* P = 0.0001; ** P = 0.0009

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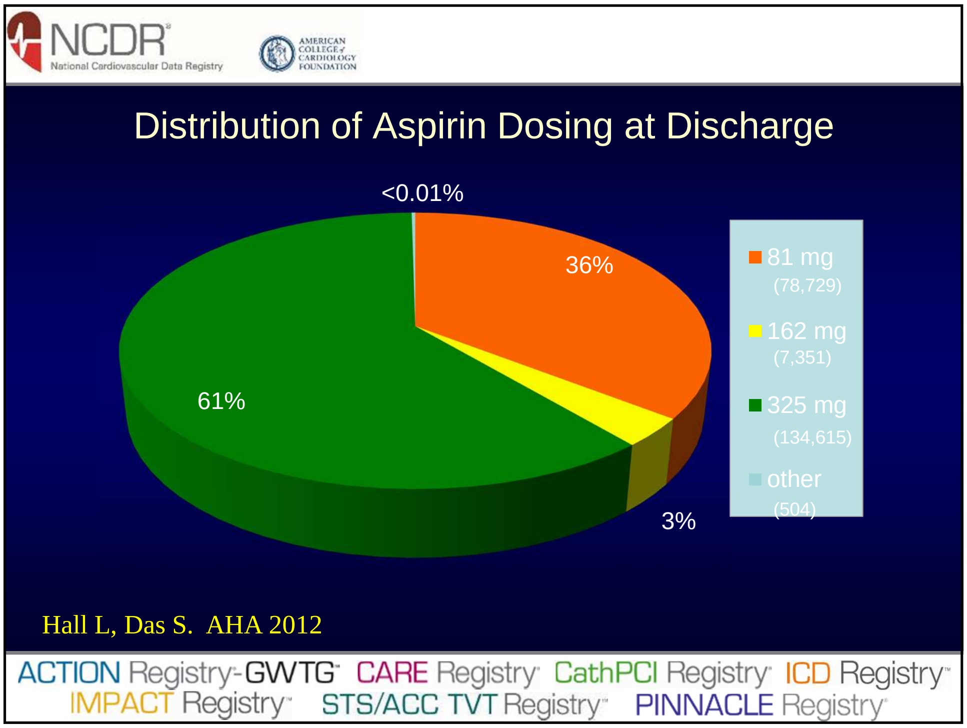
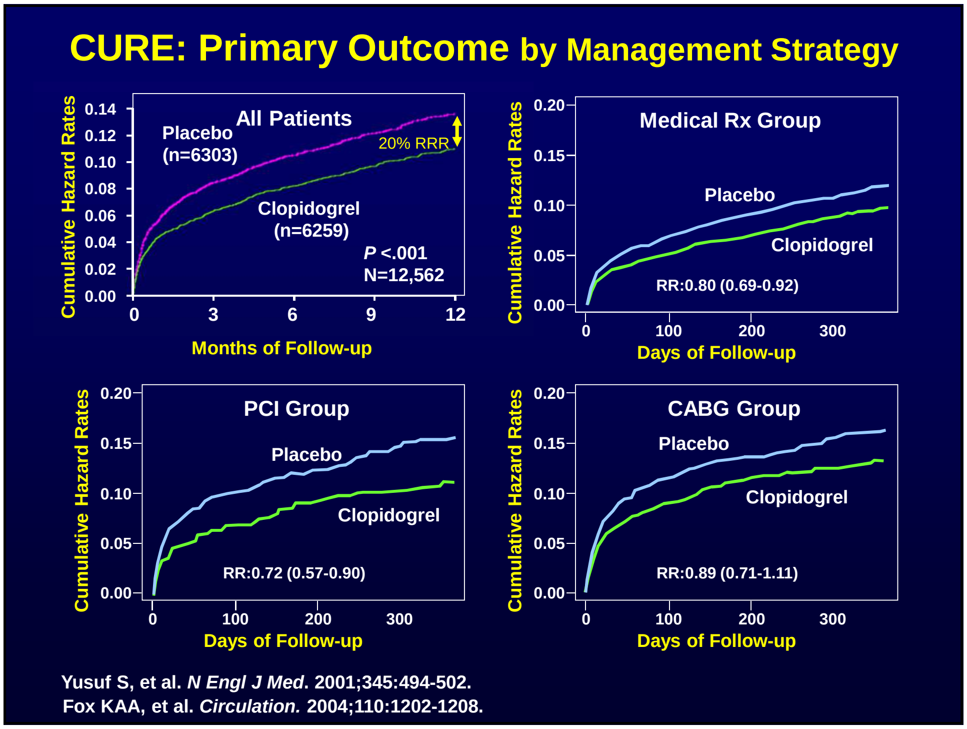


Distribution of Aspirin Dosing at Discharge

Hall L, Das S. AHA 2012



CURE: Primary Outcome by Management Strategy

Yusuf S, et al. *N Engl J Med*. 2001;345:494-502.
Fox KAA, et al. *Circulation*. 2004;110:1202-1208.

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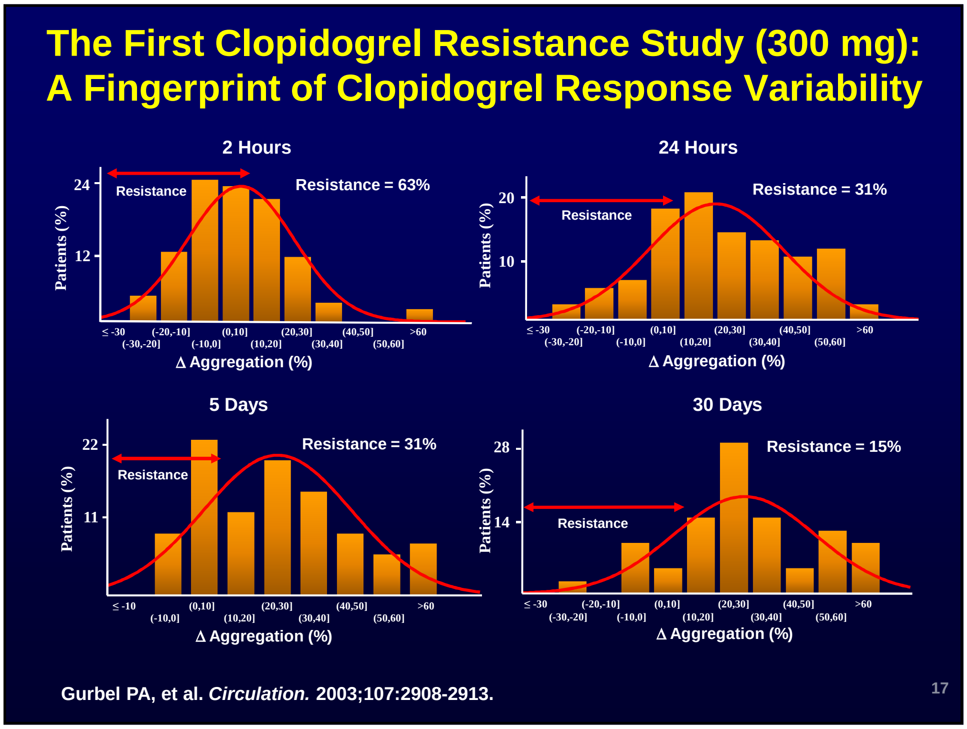
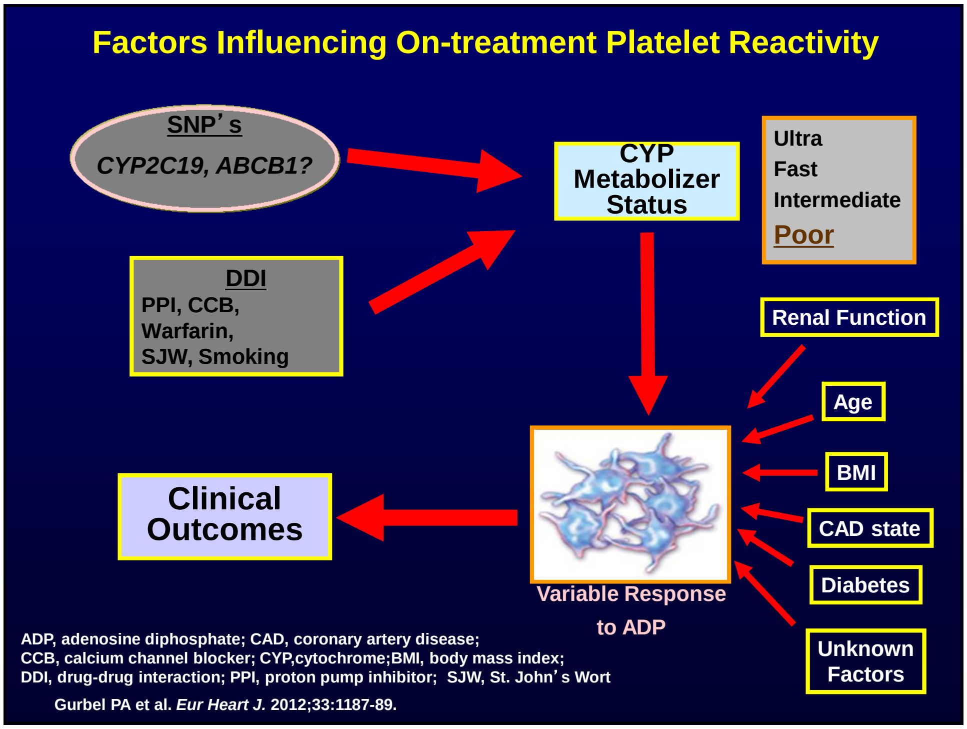


The First Clopidogrel Resistance Study (300 mg): A Fingerprint of Clopidogrel Response Variability

Gurbel PA, et al. *Circulation.* 2003;107:2908-2913.



Factors Influencing On-treatment Platelet Reactivity

SNP's
CYP2C19, ABCB1?

CYP Metabolizer Status

Ultra
Fast
Intermediate
Poor

DDI
PPI, CCB,
Warfarin,
SJW, Smoking

Renal Function

Age

BMI

CAD state

Diabetes

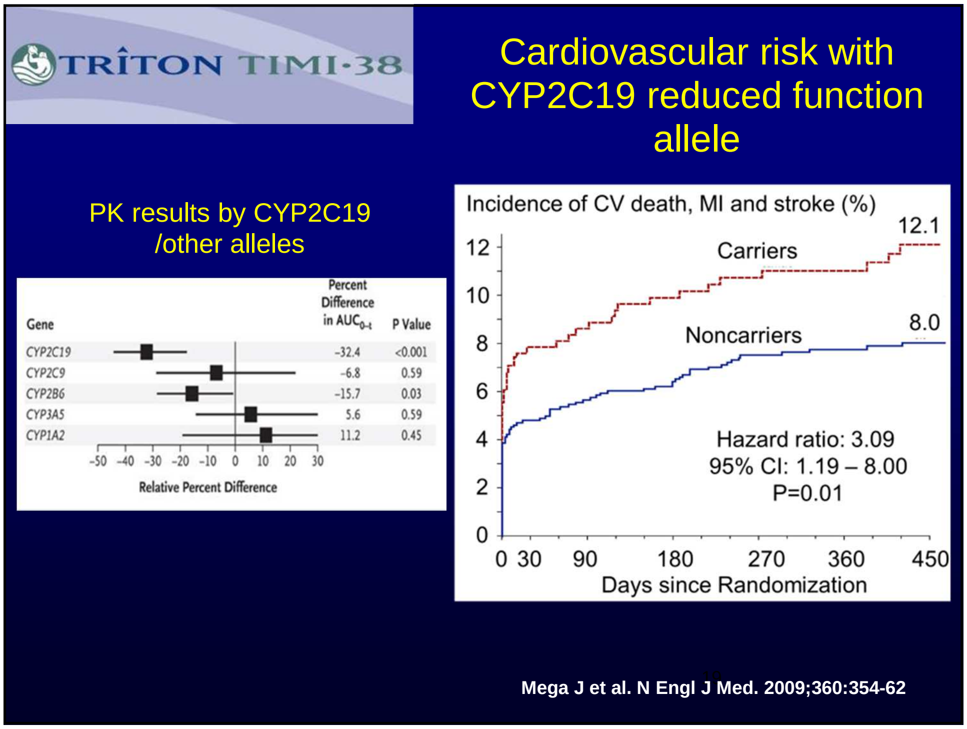
Unknown Factors

Clinical Outcomes

Variable Response to ADP

ADP, adenosine diphosphate; CAD, coronary artery disease; CCB, calcium channel blocker; CYP,cytochrome;BMI, body mass index; DDI, drug-drug interaction; PPI, proton pump inhibitor; SJW, St. John's Wort

Gurbel PA et al. *Eur Heart J.* 2012;33:1187-89.



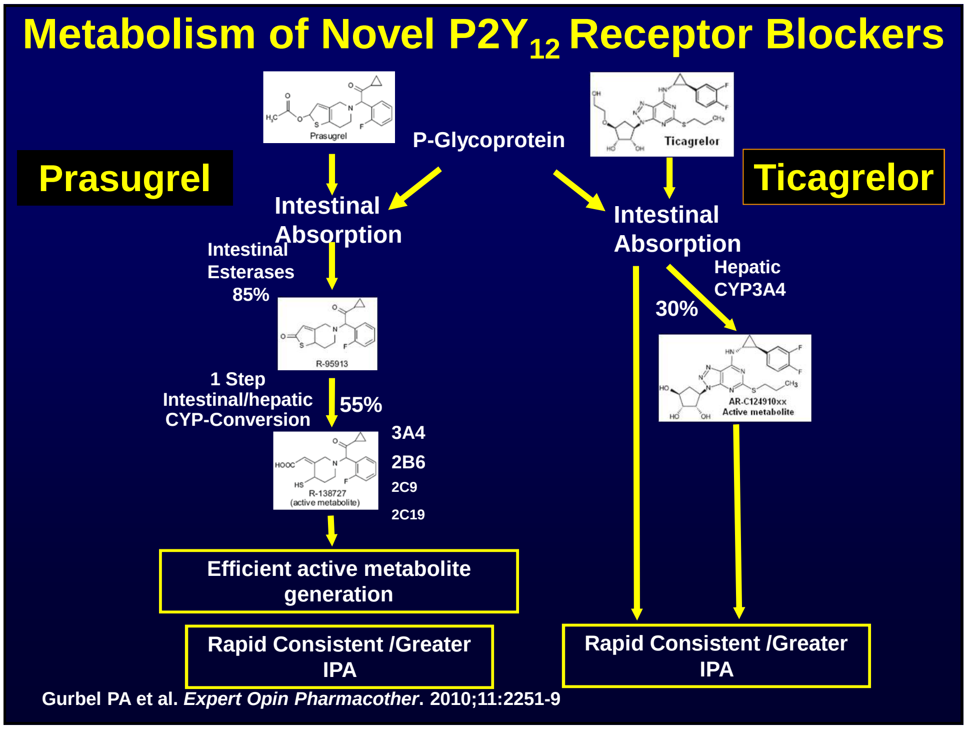
Cardiovascular risk with CYP2C19 reduced function allele

PK results by CYP2C19 /other alleles

Gene	Percent Difference in AUC$_{0-t}$	P Value
CYP2C19	−32.4	<0.001
CYP2C9	−6.8	0.59
CYP2B6	−15.7	0.03
CYP3A5	5.6	0.59
CYP1A2	11.2	0.45

Hazard ratio: 3.09
95% CI: 1.19 – 8.00
P=0.01

Mega J et al. N Engl J Med. 2009;360:354-62



Metabolism of Novel P2Y$_{12}$ Receptor Blockers

Prasugrel
R-95913
HOOC
HS
R-138727
(active metabolite)
Ticagrelor
AR-C124910xx
Active metabolite

Prasugrel

Ticagrelor

P-Glycoprotein

Intestinal Absorption

Intestinal Esterases 85%

1 Step Intestinal/hepatic CYP-Conversion

55%

3A4
2B6
2C9
2C19

Efficient active metabolite generation

Rapid Consistent /Greater IPA

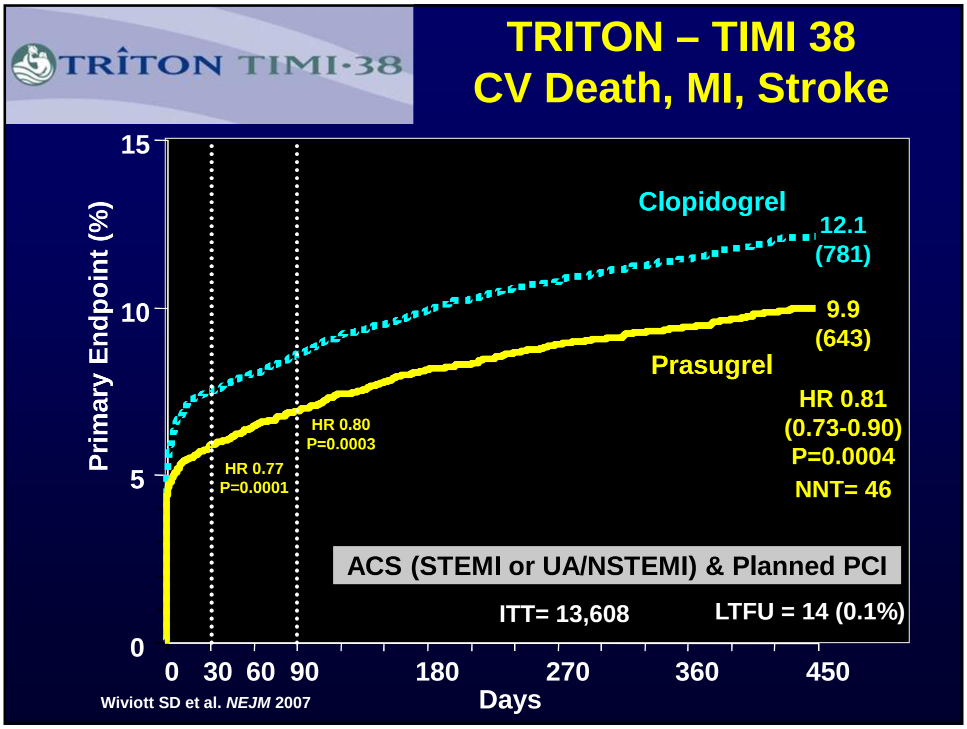
Intestinal Absorption

Hepatic CYP3A4

30%

Rapid Consistent /Greater IPA

Gurbel PA et al. *Expert Opin Pharmacother*. 2010;11:2251-9



TRITON – TIMI 38
CV Death, MI, Stroke

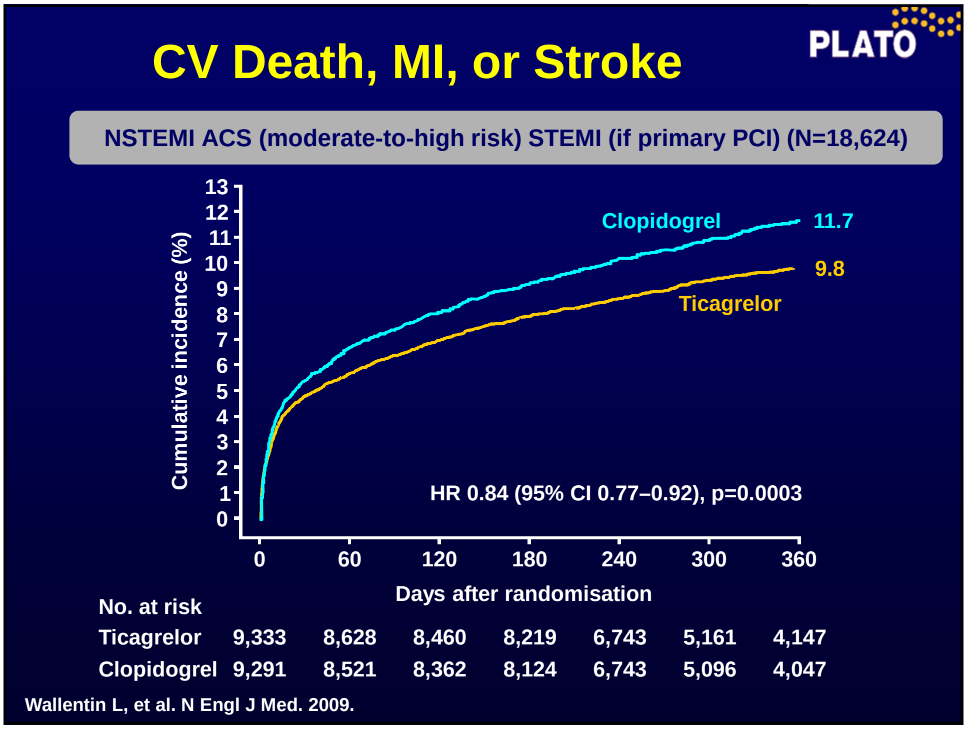
ACS (STEMI or UA/NSTEMI) & Planned PCI

ITT= 13,608

LTFU = 14 (0.1%)

HR 0.81
(0.73-0.90)
P=0.0004
NNT= 46

Wiviott SD et al. *NEJM* 2007



CV Death, MI, or Stroke

NSTEMI ACS (moderate-to-high risk) STEMI (if primary PCI) (N=18,624)

HR 0.84 (95% CI 0.77–0.92), p=0.0003

No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin L, et al. N Engl J Med. 2009.

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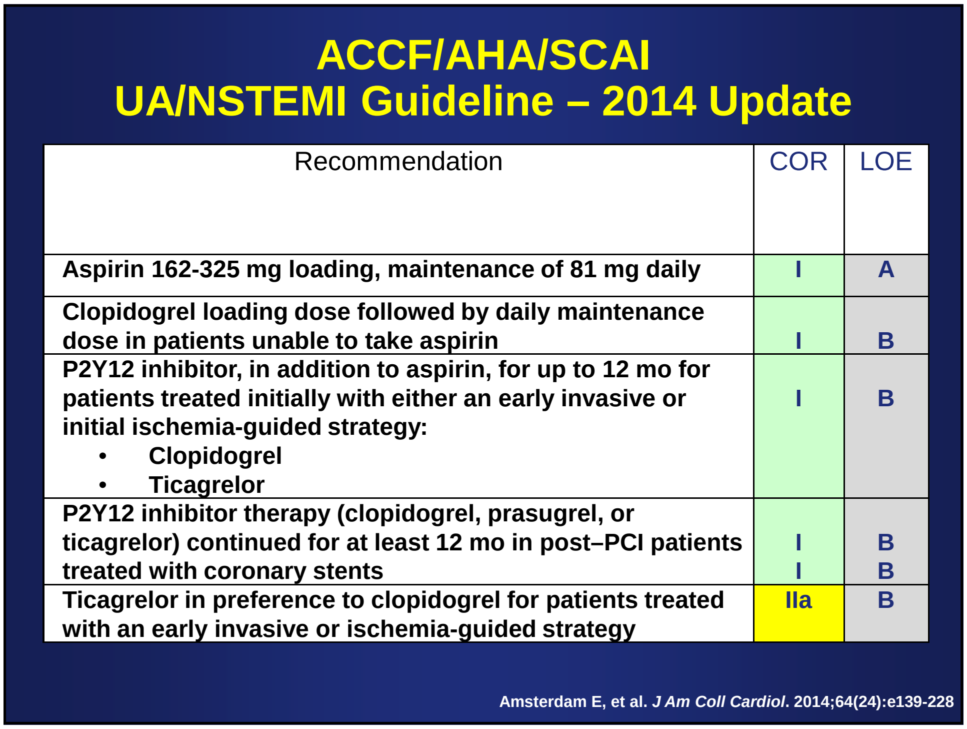
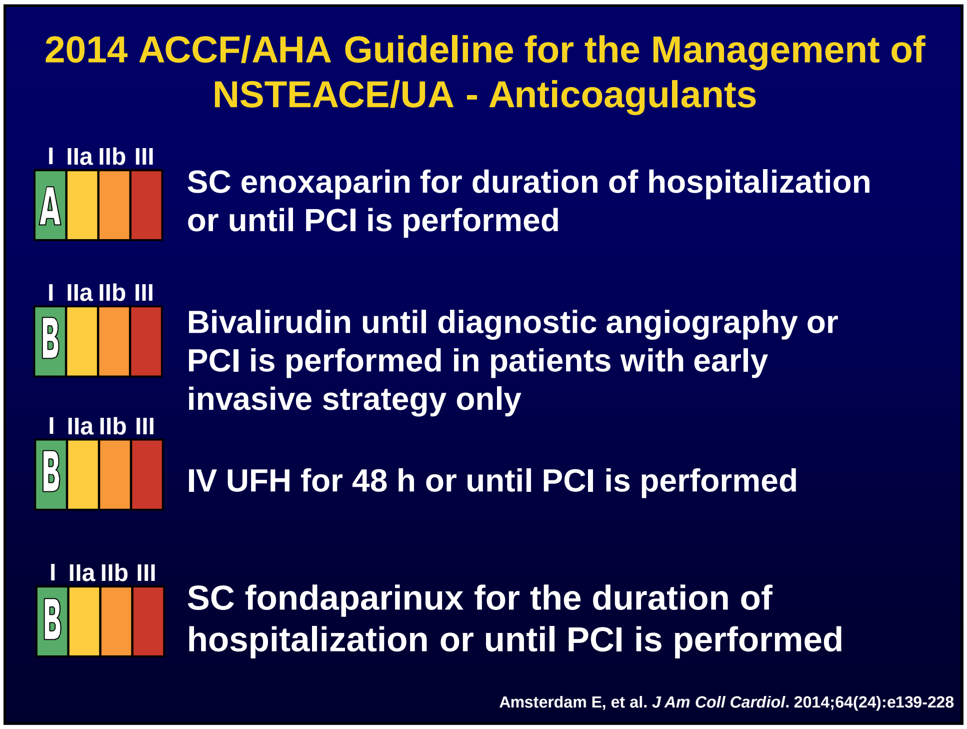


ACCF/AHA/SCAI UA/NSTEMI Guideline – 2014 Update

Recommendation	COR	LOE
Aspirin 162-325 mg loading, maintenance of 81 mg daily	**I**	**A**
Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	**I**	**B**
P2Y12 inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: • **Clopidogrel** • **Ticagrelor**	**I**	**B**
P2Y12 inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post–PCI patients treated with coronary stents	**I** **I**	**B** **B**
Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	**IIa**	**B**

Amsterdam E, et al. *J Am Coll Cardiol*. 2014;64(24):e139-228



2014 ACCF/AHA Guideline for the Management of NSTEACE/UA - Anticoagulants

I IIa IIb III
A
SC enoxaparin for duration of hospitalization or until PCI is performed

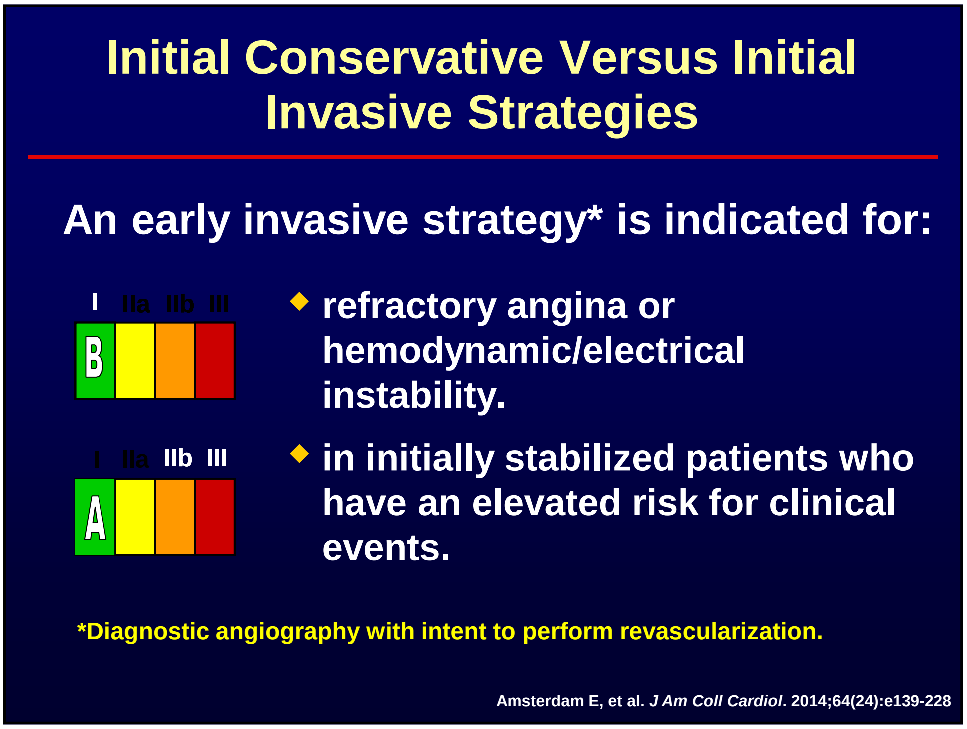
I IIa IIb III
B
Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only

I IIa IIb III
B
IV UFH for 48 h or until PCI is performed

I IIa IIb III
B
SC fondaparinux for the duration of hospitalization or until PCI is performed

Amsterdam E, et al. *J Am Coll Cardiol*. 2014;64(24):e139-228

Clinical Update in STEMI Management


I IIa IIb III
B
I IIa IIb III
A

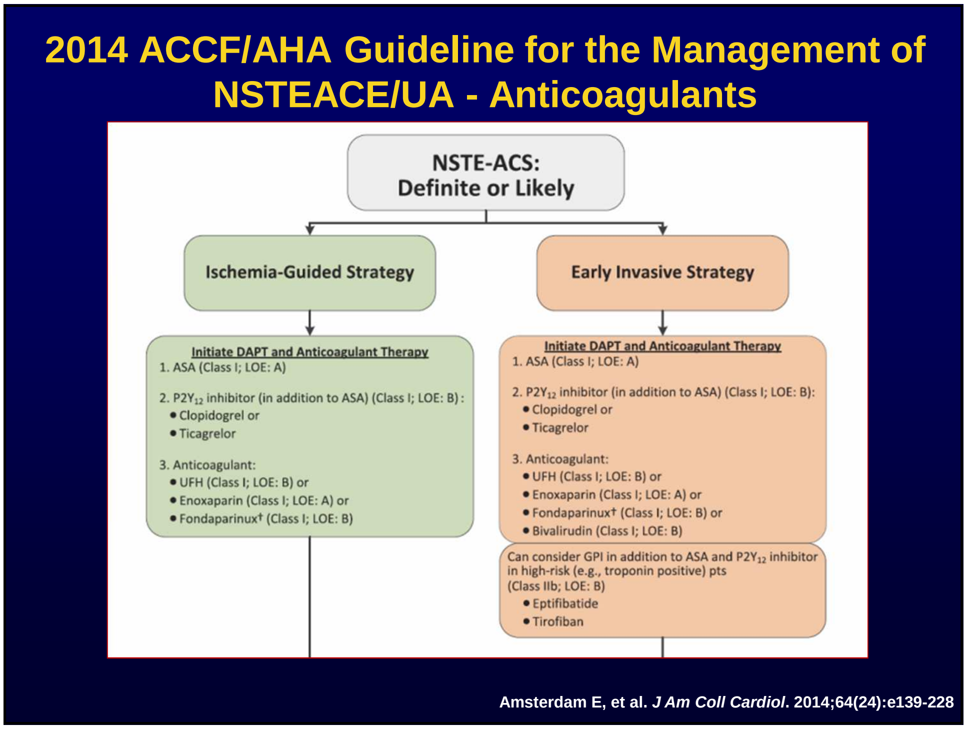
Initial Conservative Versus Initial Invasive Strategies

An early invasive strategy* is indicated for:

- refractory angina or hemodynamic/electrical instability.
- in initially stabilized patients who have an elevated risk for clinical events.

*Diagnostic angiography with intent to perform revascularization.

Amsterdam E, et al. *J Am Coll Cardiol*. 2014;64(24):e139-228



2014 ACCF/AHA Guideline for the Management of NSTEACE/UA - Anticoagulants

NSTE-ACS:
Definite or Likely

Ischemia-Guided Strategy

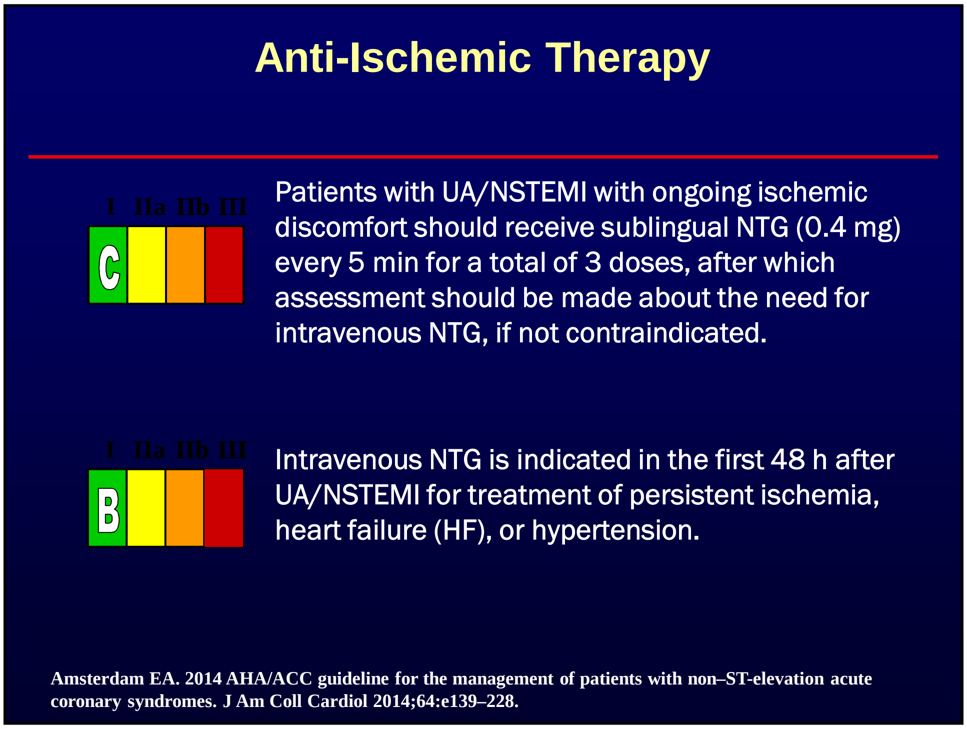
Initiate DAPT and Anticoagulant Therapy
1. ASA (Class I; LOE: A)
2. $P2Y_{12}$ inhibitor (in addition to ASA) (Class I; LOE: B) :
   - Clopidogrel or
   - Ticagrelor
3. Anticoagulant:
   - UFH (Class I; LOE: B) or
   - Enoxaparin (Class I; LOE: A) or
   - Fondaparinux† (Class I; LOE: B)

Early Invasive Strategy

Initiate DAPT and Anticoagulant Therapy
1. ASA (Class I; LOE: A)
2. $P2Y_{12}$ inhibitor (in addition to ASA) (Class I; LOE: B):
   - Clopidogrel or
   - Ticagrelor
3. Anticoagulant:
   - UFH (Class I; LOE: B) or
   - Enoxaparin (Class I; LOE: A) or
   - Fondaparinux† (Class I; LOE: B) or
   - Bivalirudin (Class I; LOE: B)

Can consider GPI in addition to ASA and $P2Y_{12}$ inhibitor in high-risk (e.g., troponin positive) pts (Class IIb; LOE: B)
- Eptifibatide
- Tirofiban

Amsterdam E, et al. *J Am Coll Cardiol*. 2014;64(24):e139-228

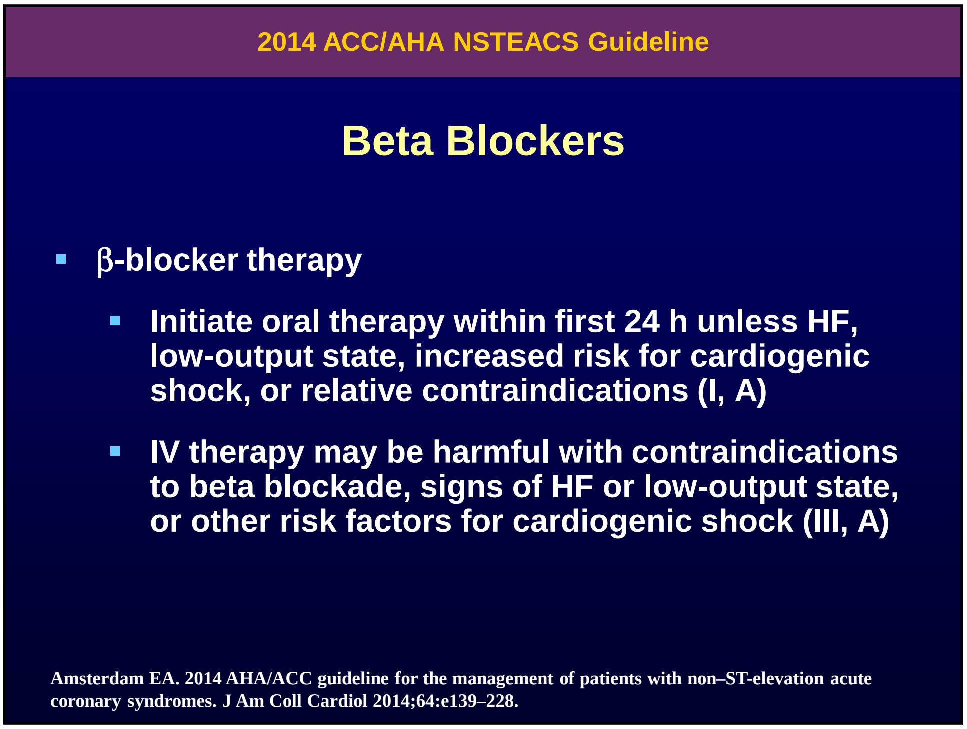

I IIa IIb III
C
I IIa IIb III
B

Anti-Ischemic Therapy

Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated.

Intravenous NTG is indicated in the first 48 h after UA/NSTEMI for treatment of persistent ischemia, heart failure (HF), or hypertension.

Amsterdam EA. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes. J Am Coll Cardiol 2014;64:e139–228.

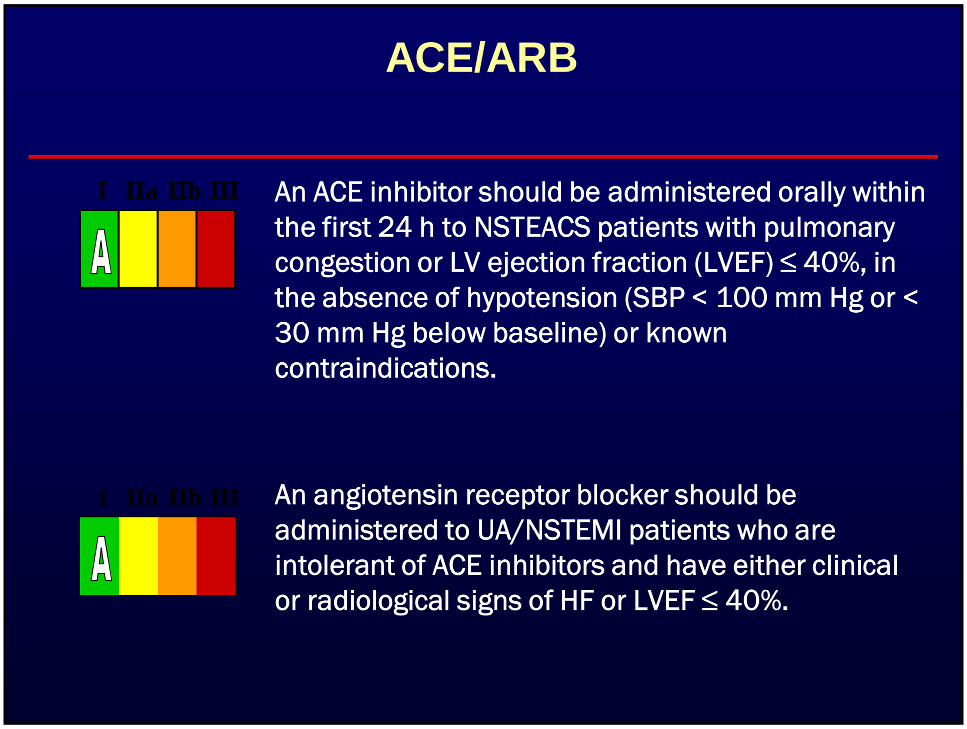


2014 ACC/AHA NSTEACS Guideline

Beta Blockers

- β-blocker therapy
  - Initiate oral therapy within first 24 h unless HF, low-output state, increased risk for cardiogenic shock, or relative contraindications (I, A)
  - IV therapy may be harmful with contraindications to beta blockade, signs of HF or low-output state, or other risk factors for cardiogenic shock (III, A)

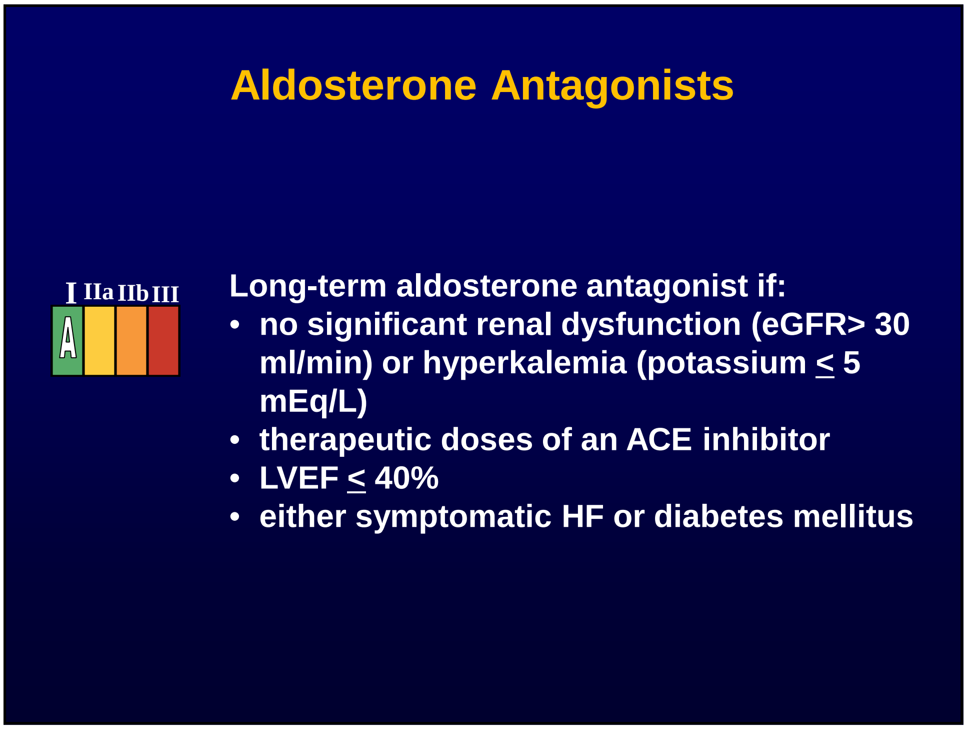
Amsterdam EA. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes. J Am Coll Cardiol 2014;64:e139–228.


I IIa IIb III
A
I IIa IIb III
A

ACE/ARB

An ACE inhibitor should be administered orally within the first 24 h to NSTEACS patients with pulmonary congestion or LV ejection fraction (LVEF) ≤ 40%, in the absence of hypotension (SBP < 100 mm Hg or < 30 mm Hg below baseline) or known contraindications.

An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of HF or LVEF ≤ 40%.


I IIa IIb III
A

Aldosterone Antagonists

Long-term aldosterone antagonist if:

- **no significant renal dysfunction (eGFR> 30 ml/min) or hyperkalemia (potassium ≤ 5 mEq/L)**
- **therapeutic doses of an ACE inhibitor**
- **LVEF ≤ 40%**
- **either symptomatic HF or diabetes mellitus**

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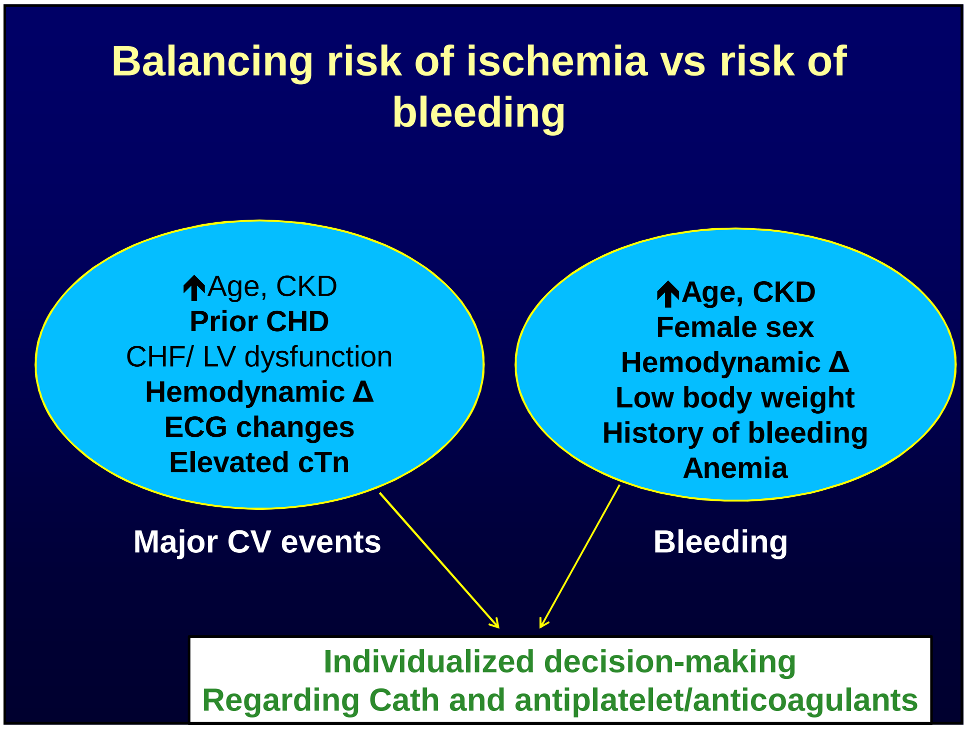


Balancing risk of ischemia vs risk of bleeding

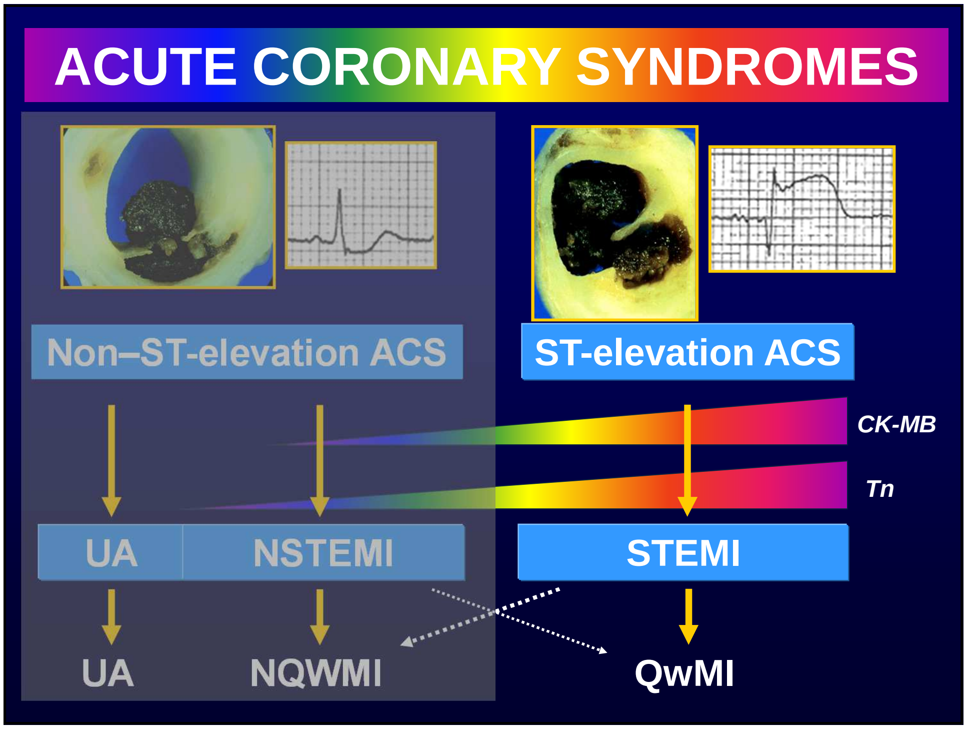
↑Age, CKD
Prior CHD
CHF/ LV dysfunction
Hemodynamic Δ
ECG changes
Elevated cTn

↑Age, CKD
Female sex
Hemodynamic Δ
Low body weight
History of bleeding
Anemia

Major CV events

Bleeding

Individualized decision-making
Regarding Cath and antiplatelet/anticoagulants



ACUTE CORONARY SYNDROMES

Non–ST-elevation ACS

ST-elevation ACS

UA | NSTEMI

STEMI

UA

NQWMI

QwMI

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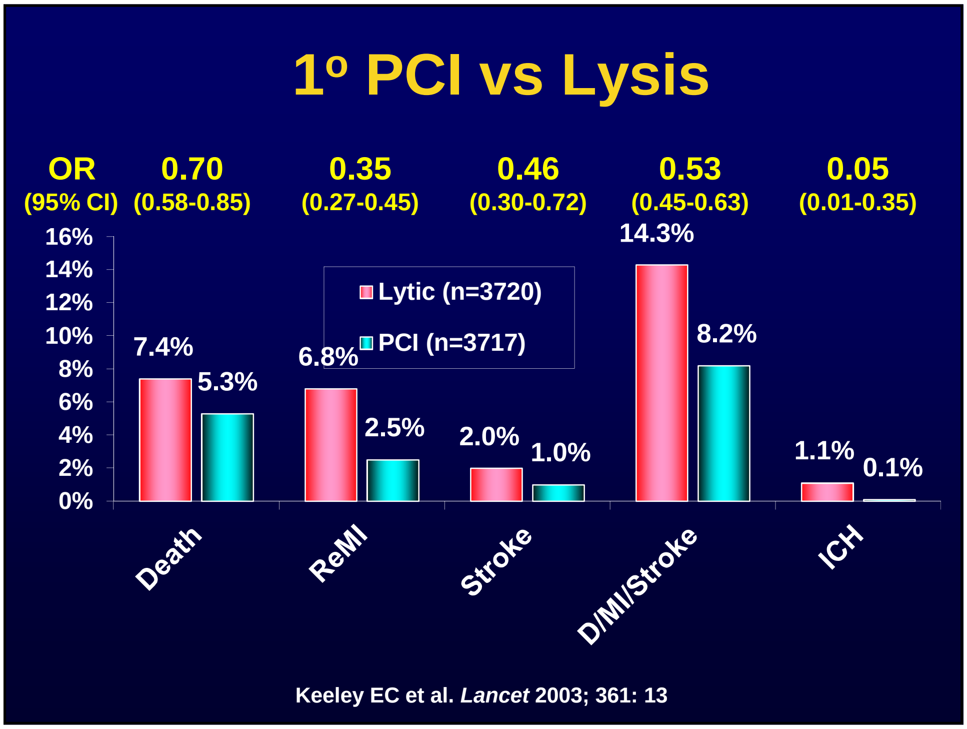
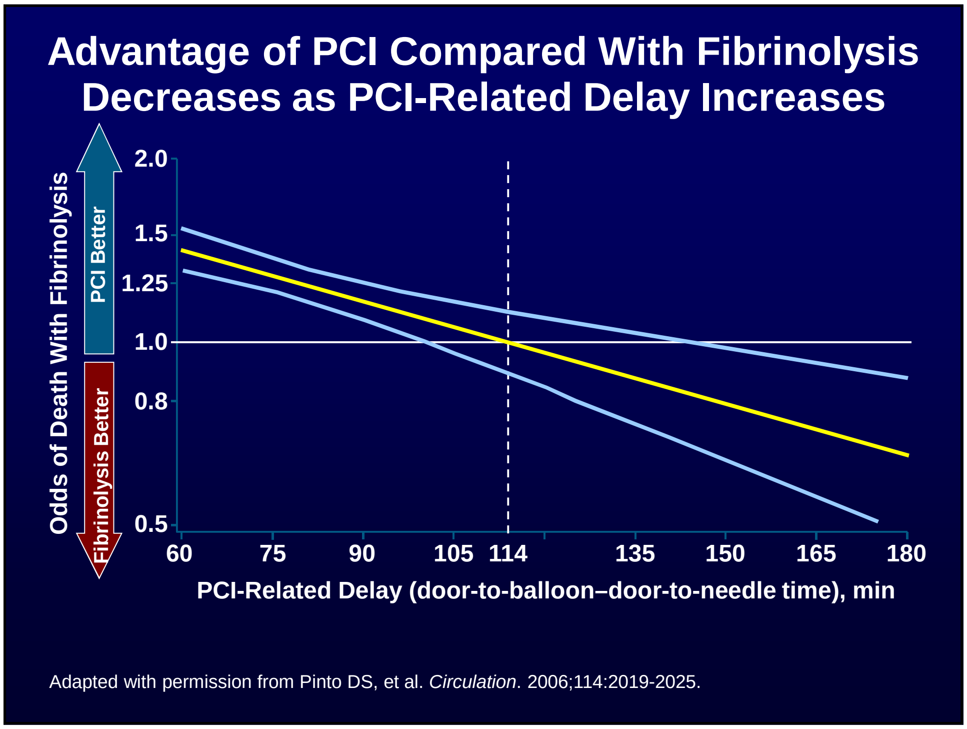
Clinical Update in STEMI Management



1º PCI vs Lysis

Keeley EC et al. *Lancet* 2003; 361: 13



Advantage of PCI Compared With Fibrinolysis Decreases as PCI-Related Delay Increases

Adapted with permission from Pinto DS, et al. *Circulation*. 2006;114:2019-2025.

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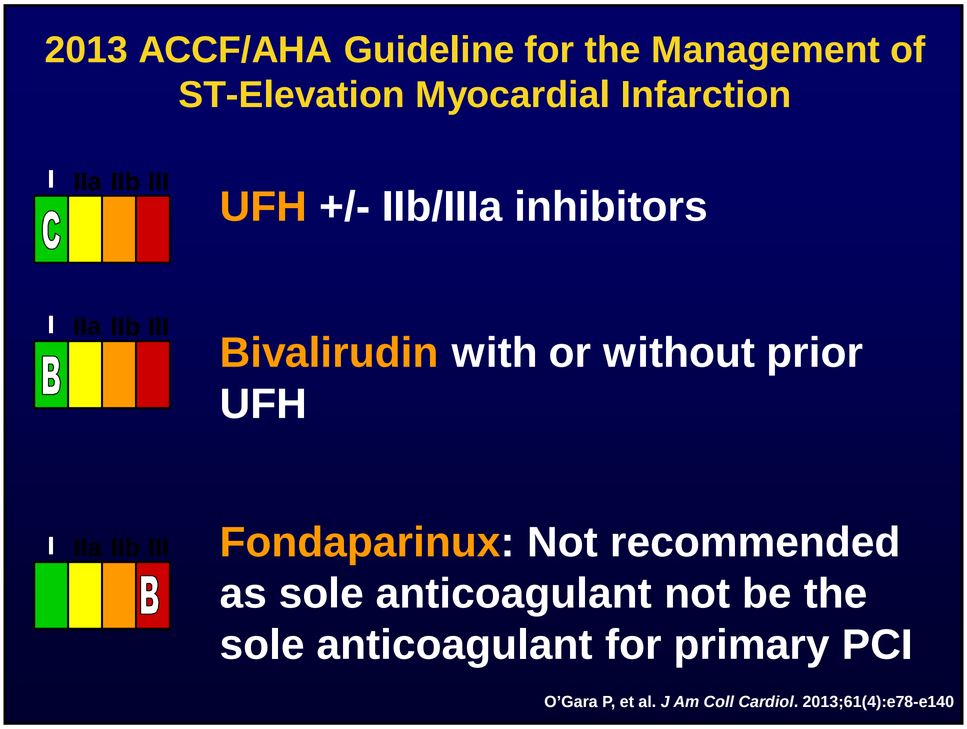


2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

I IIa IIb III
C

UFH +/- IIb/IIIa inhibitors

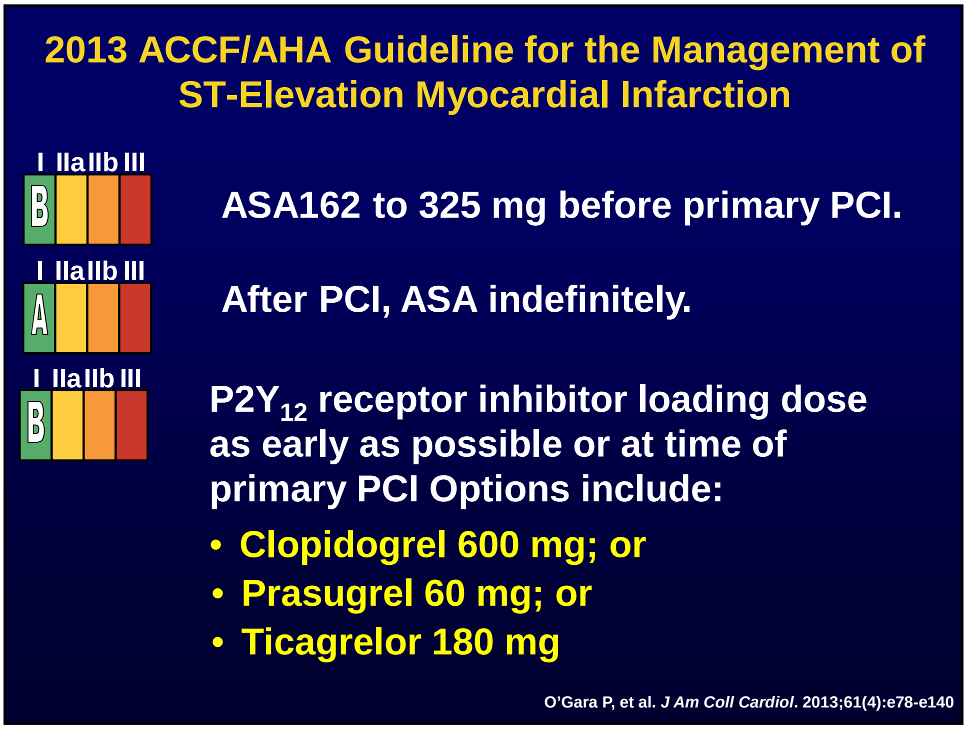
I IIa IIb III
B

Bivalirudin with or without prior UFH

I IIa IIb III
B

Fondaparinux: Not recommended as sole anticoagulant not be the sole anticoagulant for primary PCI

O'Gara P, et al. *J Am Coll Cardiol*. 2013;61(4):e78-e140



2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

I IIa IIb III
B

ASA162 to 325 mg before primary PCI.

I IIa IIb III
A

After PCI, ASA indefinitely.

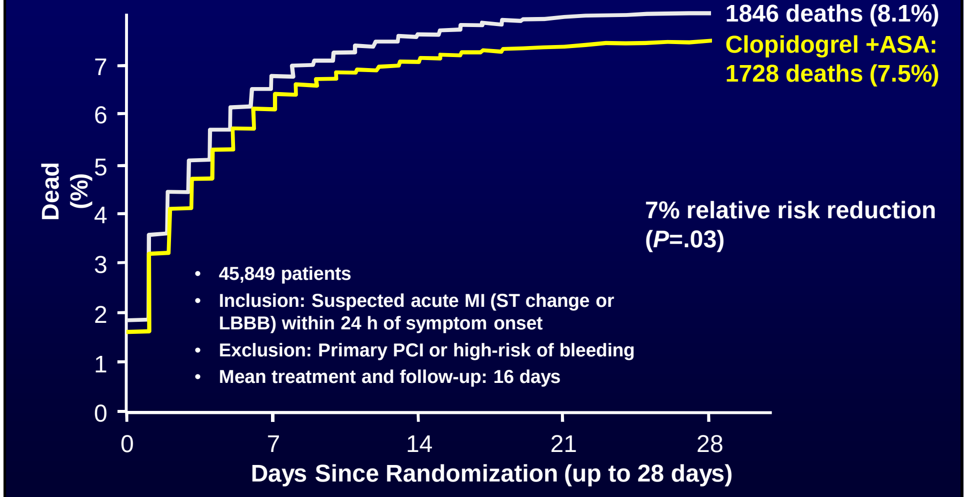
I IIa IIb III
B

$P2Y_{12}$ receptor inhibitor loading dose as early as possible or at time of primary PCI Options include:

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

O'Gara P, et al. *J Am Coll Cardiol*. 2013;61(4):e78-e140

COMMIT: Effect of Clopidogrel on Death in Hospital



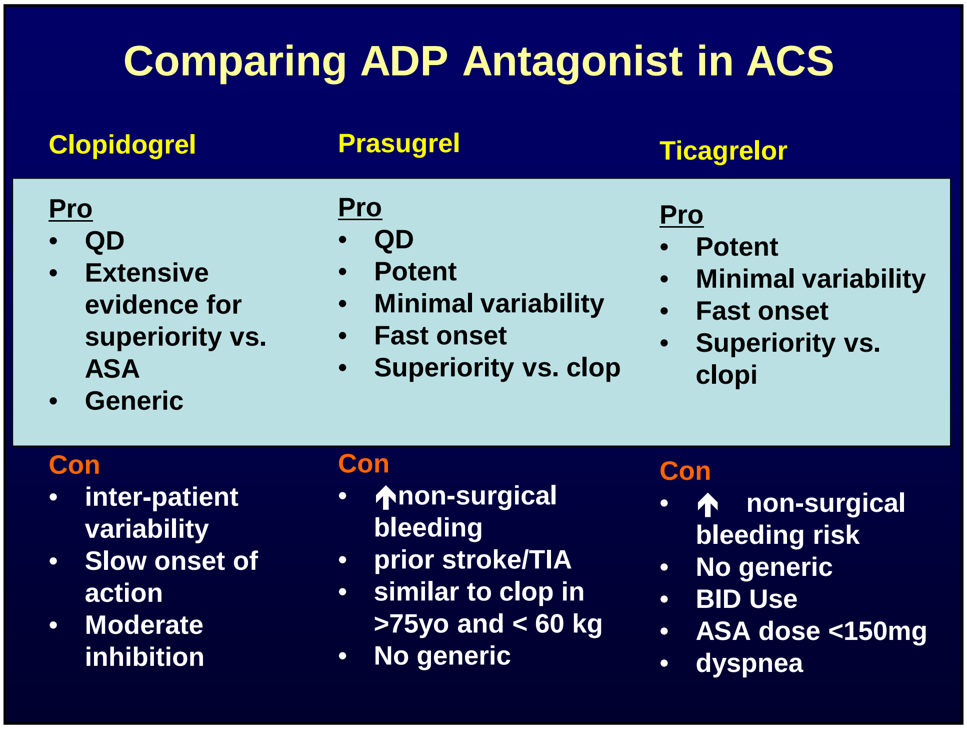
7% relative risk reduction (*P*=.03)

- 45,849 patients
- Inclusion: Suspected acute MI (ST change or LBBB) within 24 h of symptom onset
- Exclusion: Primary PCI or high-risk of bleeding
- Mean treatment and follow-up: 16 days

Chen et al. *Lancet.* 2005;366:1607-1621

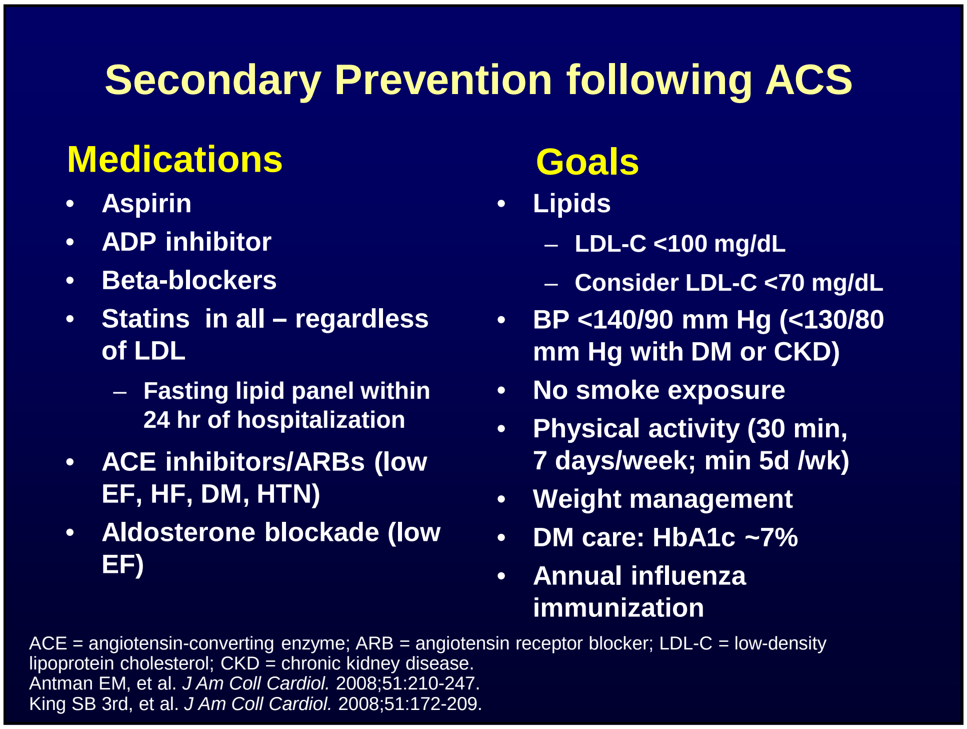
Summary for STEMI

- Aspirin for everyone
- Decide early on reperfusion strategy
- If 1° PCI
  - D-to-B <90 minutes
  - Clopidogrel (600 mg) or Prasugrel (60mg) or Ticagrelor (180 mg)
  - UFH, Enox, Bival
- If Lytics
  - D-to-N <30 minutes
  - Clopidogrel (300 mg for < 75yo, 75 mg for all)
  - Enoxaparin or Fondaparinux or UFH
  - Monitor ST Resolution for reperfusion
- Beta-blockers if no signs of HF or shock
- Early ACEI/ARB for EF <40% or signs of HF



Comparing ADP Antagonist in ACS

	Clopidogrel	Prasugrel	Ticagrelor
Pro	QD Extensive evidence for superiority vs. ASA Generic	QD Potent Minimal variability Fast onset Superiority vs. clop	Potent Minimal variability Fast onset Superiority vs. clopi
Con	inter-patient variability Slow onset of action Moderate inhibition	↑non-surgical bleeding prior stroke/TIA similar to clop in >75yo and < 60 kg No generic	↑ non-surgical bleeding risk No generic BID Use ASA dose <150mg dyspnea



Secondary Prevention following ACS

Medications

- Aspirin
- ADP inhibitor
- Beta-blockers
- Statins in all – regardless of LDL
  - Fasting lipid panel within 24 hr of hospitalization
- ACE inhibitors/ARBs (low EF, HF, DM, HTN)
- Aldosterone blockade (low EF)

Goals

- Lipids
  - LDL-C <100 mg/dL
  - Consider LDL-C <70 mg/dL
- BP <140/90 mm Hg (<130/80 mm Hg with DM or CKD)
- No smoke exposure
- Physical activity (30 min, 7 days/week; min 5d /wk)
- Weight management
- DM care: HbA1c ~7%
- Annual influenza immunization

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LDL-C = low-density lipoprotein cholesterol; CKD = chronic kidney disease.
Antman EM, et al. *J Am Coll Cardiol.* 2008;51:210-247.
King SB 3rd, et al. *J Am Coll Cardiol.* 2008;51:172-209.

2013 ACCF/AHA Guideline for the Management of STEMI – Cardiac Arrest

I IIa IIb III
B

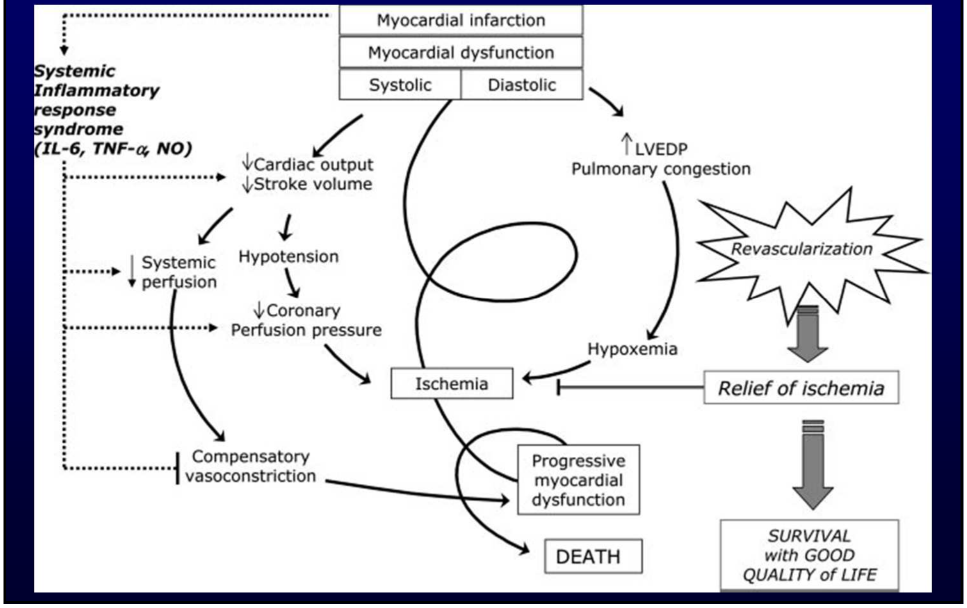
Therapeutic hypothermia should be started as soon as possible in comatose patients with STEMI and out-of-hospital cardiac arrest caused by VF or pulseless VT, including patients who undergo primary PCI.

I IIa IIb III
B

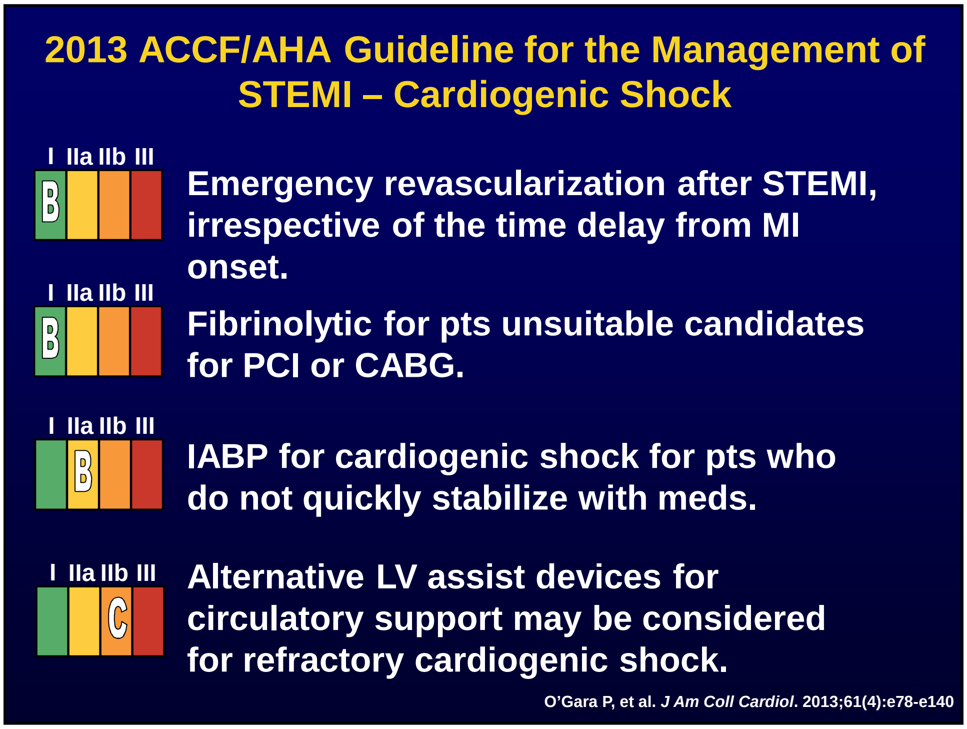
Immediate angiography and PCI when indicated should be performed in resuscitated out-of-hospital cardiac arrest patients whose initial ECG shows STEMI.

O'Gara P, et al. *J Am Coll Cardiol*. 2013;61(4):e78-e140

Cardiogenic Shock


Myocardial infarction
Myocardial dysfunction
Systolic
Diastolic
Systemic Inflammatory response syndrome (IL-6, TNF-α, NO)
↓Cardiac output
↓Stroke volume
↑LVEDP
Pulmonary congestion
↓Systemic perfusion
Hypotension
Revascularization
↓Coronary Perfusion pressure
Hypoxemia
Ischemia
Relief of ischemia
Compensatory vasoconstriction
Progressive myocardial dysfunction
DEATH
SURVIVAL with GOOD QUALITY of LIFE

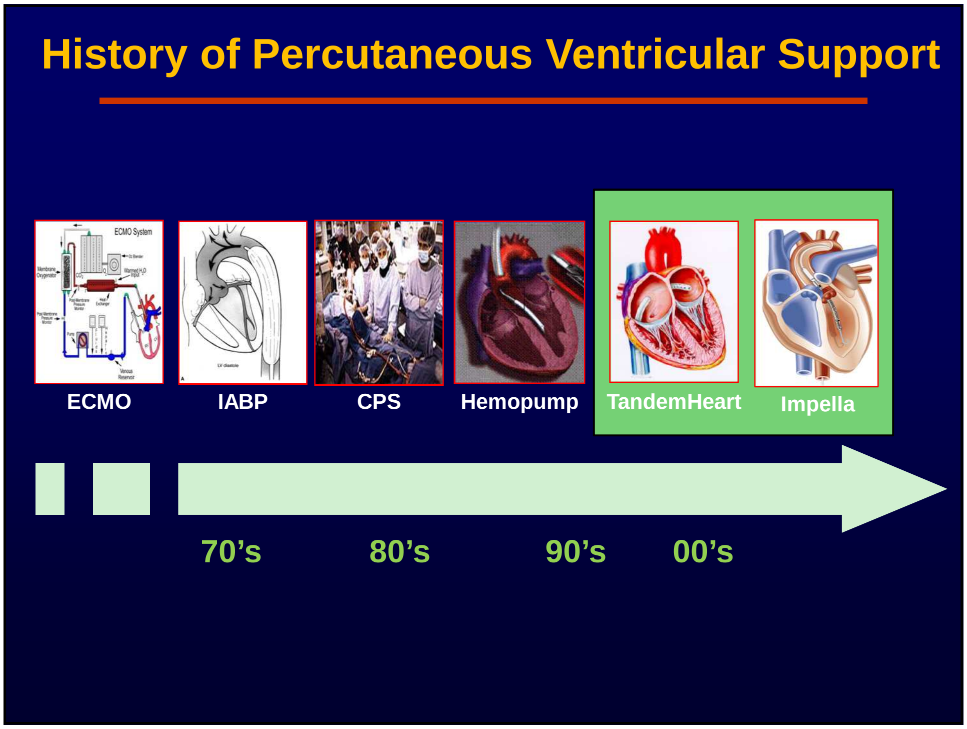
Clinical Update in STEMI Management



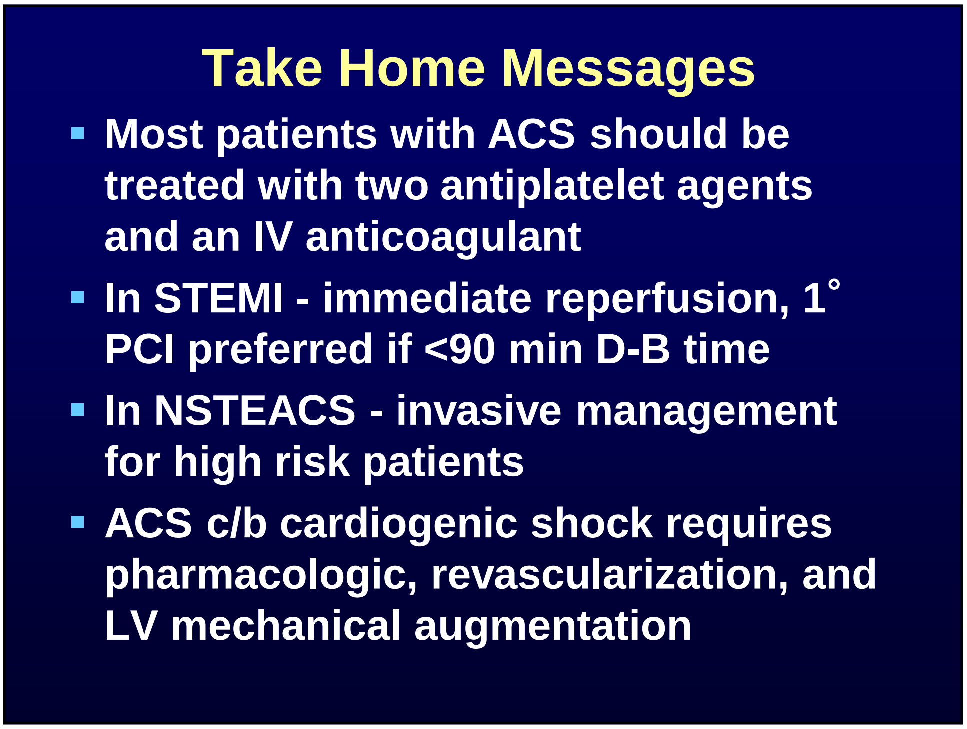
2013 ACCF/AHA Guideline for the Management of STEMI – Cardiogenic Shock

I	IIa	IIb	III	
B				Emergency revascularization after STEMI, irrespective of the time delay from MI onset.
B				Fibrinolytic for pts unsuitable candidates for PCI or CABG.
	B			IABP for cardiogenic shock for pts who do not quickly stabilize with meds.
		C		Alternative LV assist devices for circulatory support may be considered for refractory cardiogenic shock.

O'Gara P, et al. *J Am Coll Cardiol*. 2013;61(4):e78-e140

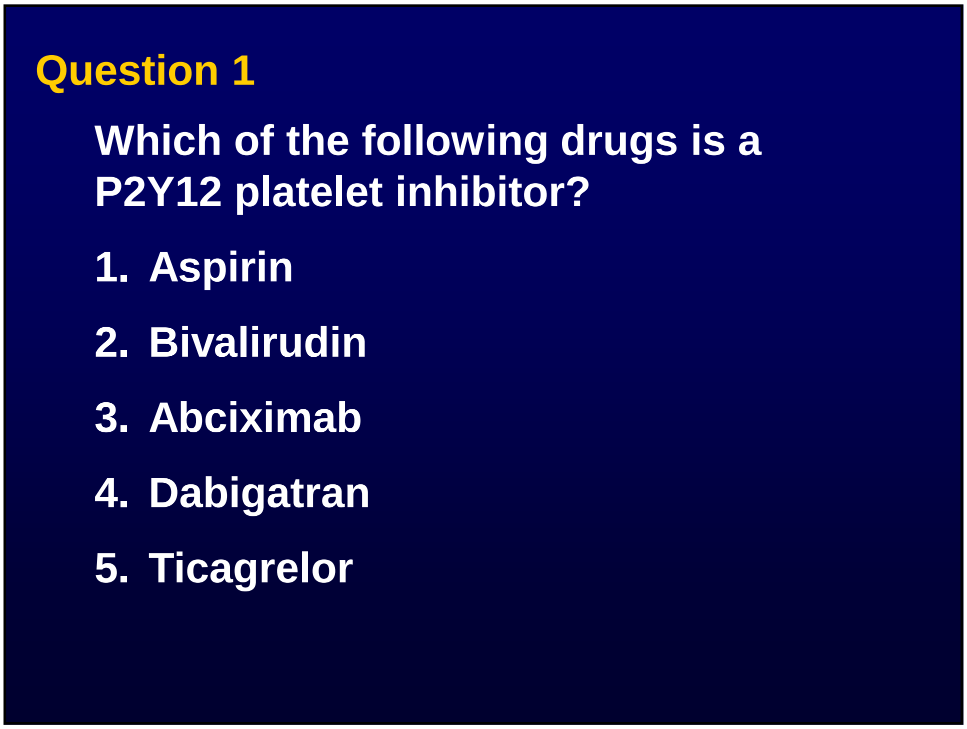


History of Percutaneous Ventricular Support



Take Home Messages

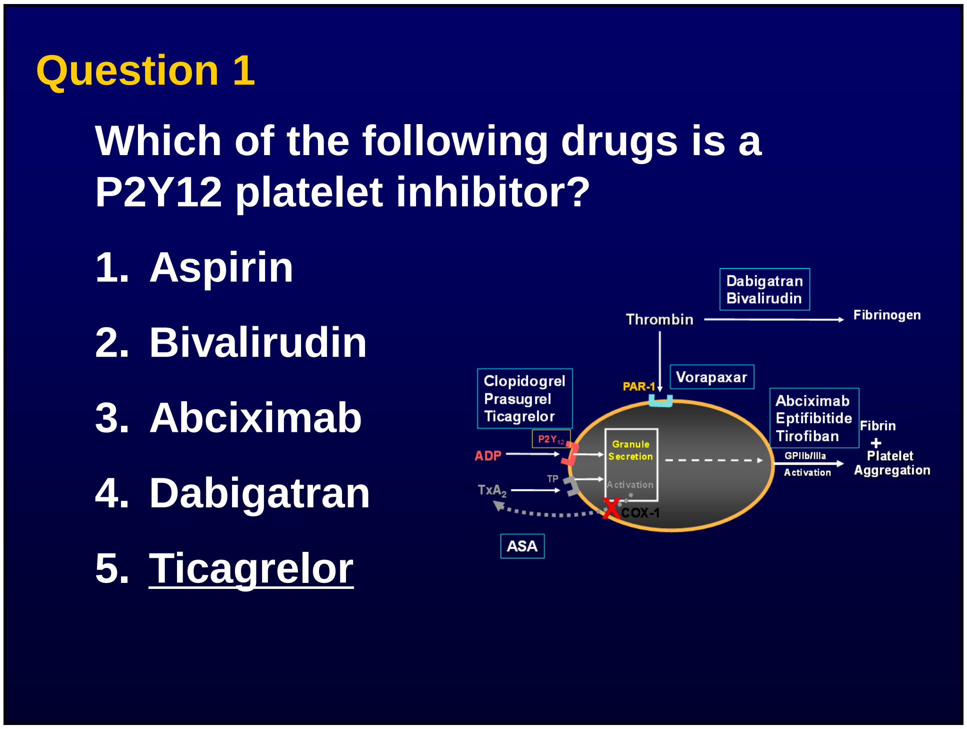
- Most patients with ACS should be treated with two antiplatelet agents and an IV anticoagulant
- In STEMI - immediate reperfusion, 1° PCI preferred if <90 min D-B time
- In NSTEACS - invasive management for high risk patients
- ACS c/b cardiogenic shock requires pharmacologic, revascularization, and LV mechanical augmentation



Question 1

Which of the following drugs is a P2Y12 platelet inhibitor?

1. Aspirin
2. Bivalirudin
3. Abciximab
4. Dabigatran
5. Ticagrelor

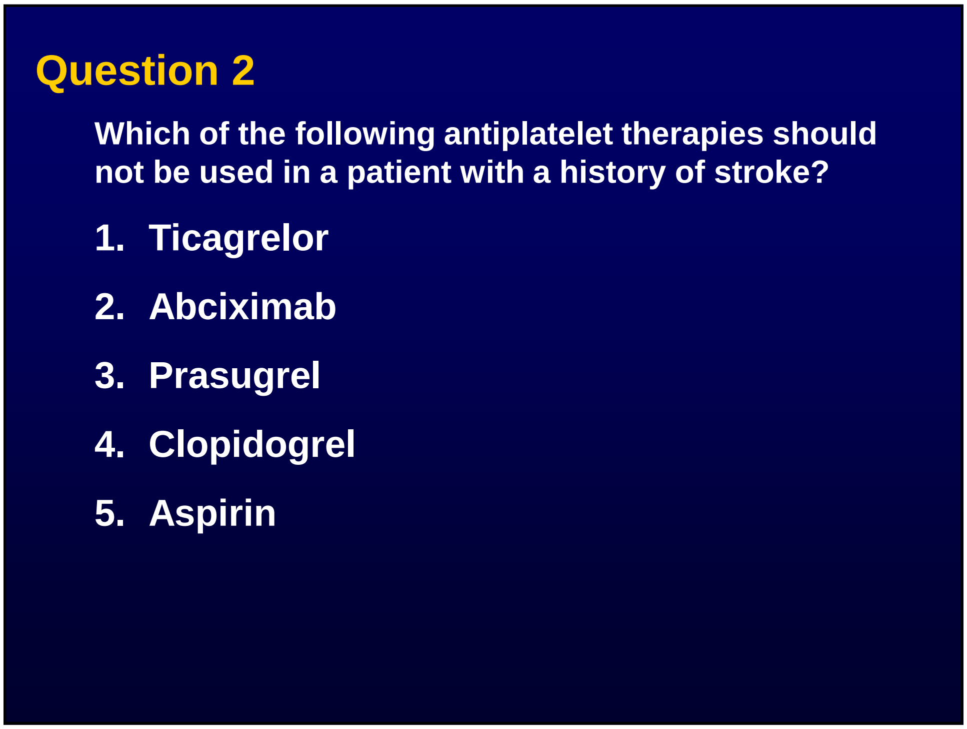


Question 1

Which of the following drugs is a P2Y12 platelet inhibitor?

1. Aspirin
2. Bivalirudin
3. Abciximab
4. Dabigatran
5. Ticagrelor

Dabigatran
Bivalirudin
Thrombin
Fibrinogen
Clopidogrel
Prasugrel
Ticagrelor
PAR-1
Vorapaxar
Abciximab
Eptifibitide
Tirofiban
Fibrin
+
Platelet
Aggregation
P2Y12
ADP
Granule
Secretion
GPIIb/IIIa
Activation
TP
TxA2
Activation
COX-1
ASA



Question 2

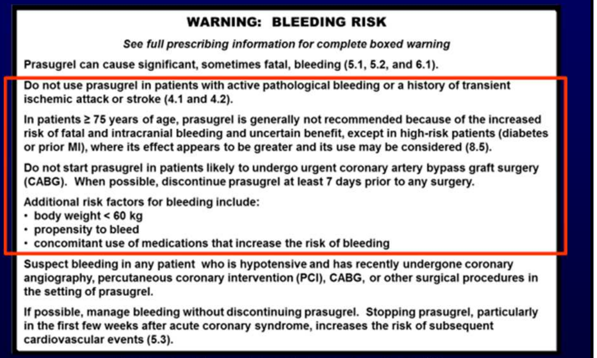
Which of the following antiplatelet therapies should not be used in a patient with a history of stroke?

1. Ticagrelor
2. Abciximab
3. Prasugrel
4. Clopidogrel
5. Aspirin

Question 2

Which of the following antiplatelet therapies should not be used in a patient with a history of stroke?

1. Ticagrelor
2. Abciximab
3. Prasugrel
4. Clopidogrel
5. Aspirin



WARNING: BLEEDING RISK

See full prescribing information for complete boxed warning

Prasugrel can cause significant, sometimes fatal, bleeding (5.1, 5.2, and 6.1).

Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke (4.1 and 4.2).

In patients ≥ 75 years of age, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered (8.5).

Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue prasugrel at least 7 days prior to any surgery.

Additional risk factors for bleeding include:
- body weight < 60 kg
- propensity to bleed
- concomitant use of medications that increase the risk of bleeding

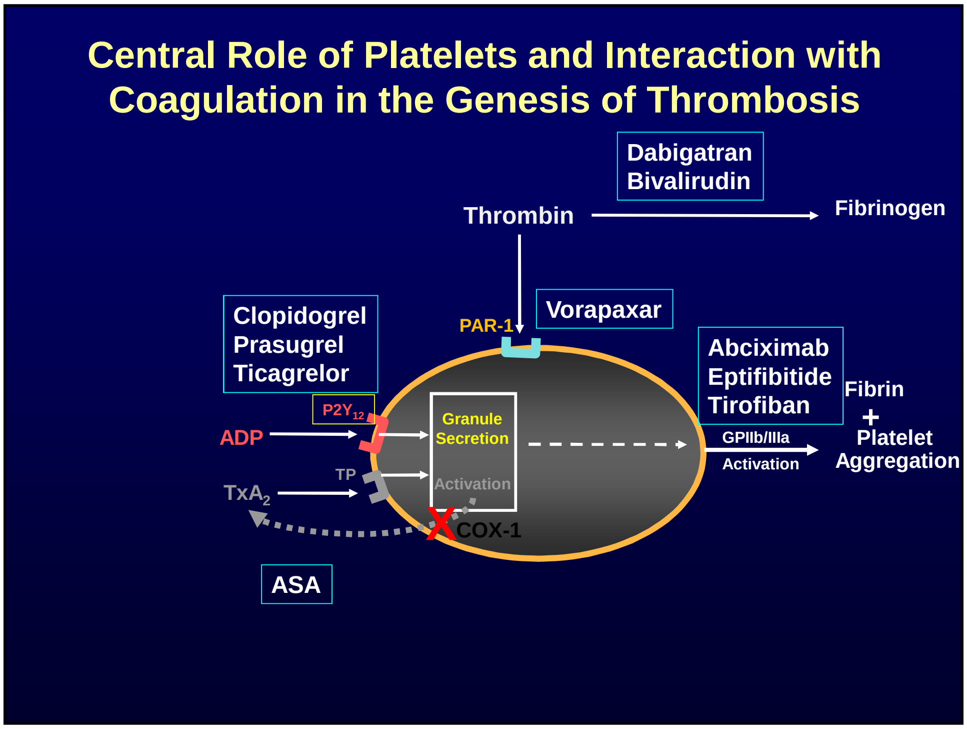
Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of prasugrel.

If possible, manage bleeding without discontinuing prasugrel. Stopping prasugrel, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events (5.3).

http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=46002600

References

- Amsterdam EA, et al. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–228.
- O'Gara PT, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Circulation. 2013;127(4):e362-425. Epub 2012/12/19.
- Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation. 2008;117(5):686-97. Epub 2008/02/06.
- Steg PG, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569-619. Epub 2012/08/28.



Central Role of Platelets and Interaction with Coagulation in the Genesis of Thrombosis

Dabigatran
Bivalirudin
Thrombin
Fibrinogen
Clopidogrel
Prasugrel
Ticagrelor
Vorapaxar
PAR-1
Abciximab
Eptifibitide
Tirofiban
Fibrin
+
Platelet
Aggregation
P2Y$_{12}$
ADP
Granule
Secretion
GPIIb/IIIa
Activation
TP
TxA$_2$
Activation
X
COX-1
ASA

Benjamin M. Scirica, MD, MPH

Arrhythmias

Melanie Maytin, MD
BWH Cardiac Arrhythmia Service
Instructor of Medicine, Harvard Medical School

Conflict of Interest

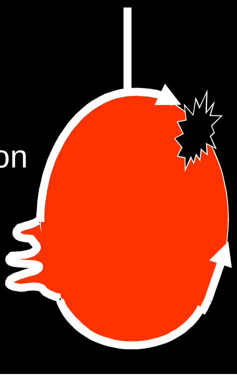
No conflicts of interest relevant to this presentation to disclose

Overview

- Tachycardias
  - – Pathophysiology – rhythms and drugs
  - – General approach to tachyarrhythmias
  - – Supraventricular tachycardias
  - – Ventricular tachyarrhythmias
  - – Syndromes worth hearing about
- Bradycardia

Tachyarrhythmia Pathophysiology

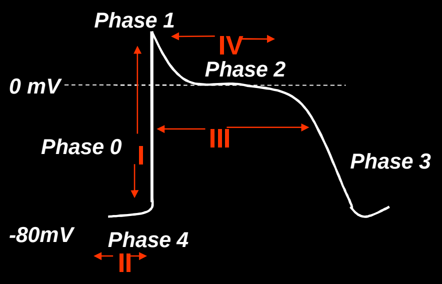
- Automaticity
- Triggered activity
  - – Secondary depolarizations / oscillation in membrane potential
- Re-entry –
  - – Unidirectional block
  - – Area of slow conduction
  - – Two separate pathways for conduction
    - Dual node physiology
    - Bypass tract
    - Scar → multiple circuits

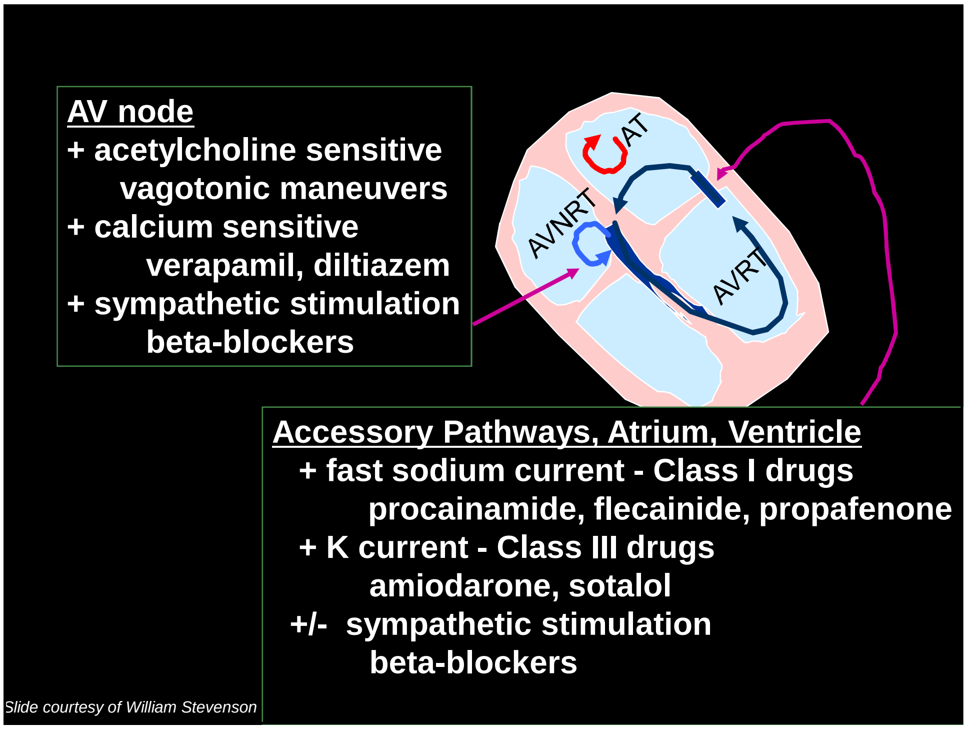


Antiarrhythmics

Vaughan Williams classification of antiarrhythmic drugs

- **Class I:** block sodium channels
  - Ia (quinidine, procainamide, disopyramide) ↑AP
  - Ib (lidocaine) ↓AP
  - Ic (flecainide) ≠AP
- **Class II:** ß-adrenoceptor antagonists (atenolol, sotalol)
- **Class III:** K channel blockers, prolong action potential and prolong refractory period (amiodarone, sotalol)
- **Class IV:** Calcium channel antagonists. Impair impulse propagation in nodal and damaged areas (verapamil)


Phase 1
IV
Phase 2
0 mV
III
Phase 0
I
Phase 3
-80mV
Phase 4
II



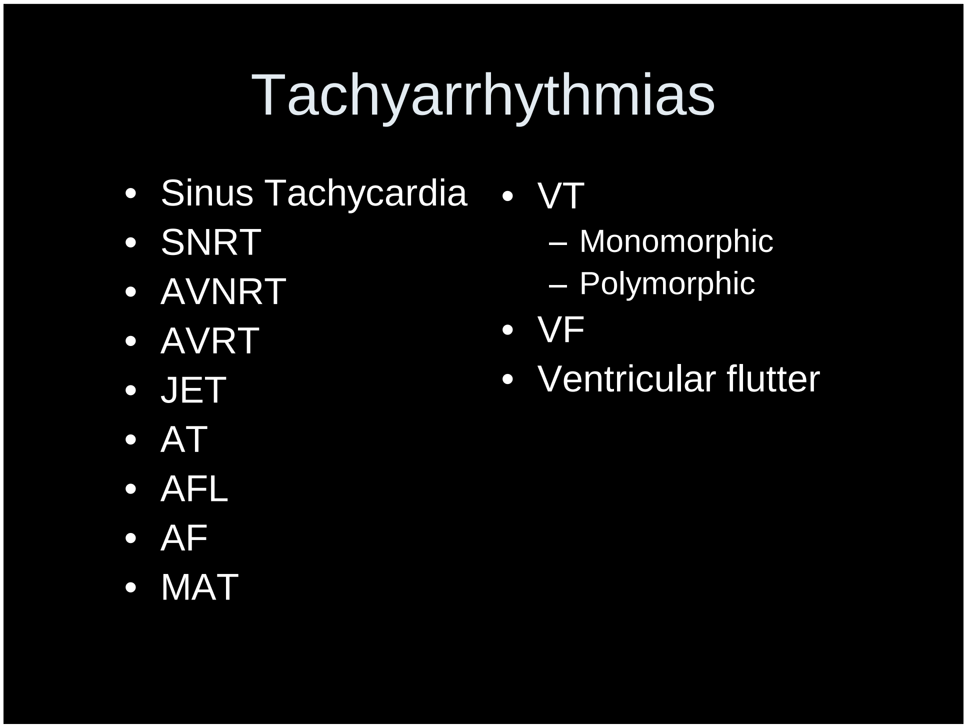
AV node

+ acetylcholine sensitive
  vagotonic maneuvers
+ calcium sensitive
  verapamil, diltiazem
+ sympathetic stimulation
  beta-blockers

Accessory Pathways, Atrium, Ventricle

+ fast sodium current - Class I drugs
  procainamide, flecainide, propafenone
+ K current - Class III drugs
  amiodarone, sotalol
+/- sympathetic stimulation
  beta-blockers

Slide courtesy of William Stevenson

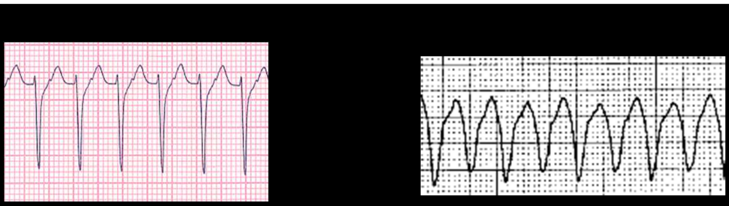


Tachyarrhythmias

- Sinus Tachycardia
- SNRT
- AVNRT
- AVRT
- JET
- AT
- AFL
- AF
- MAT
- VT
  - Monomorphic
  - Polymorphic
- VF
- Ventricular flutter

Is there time to think about it?

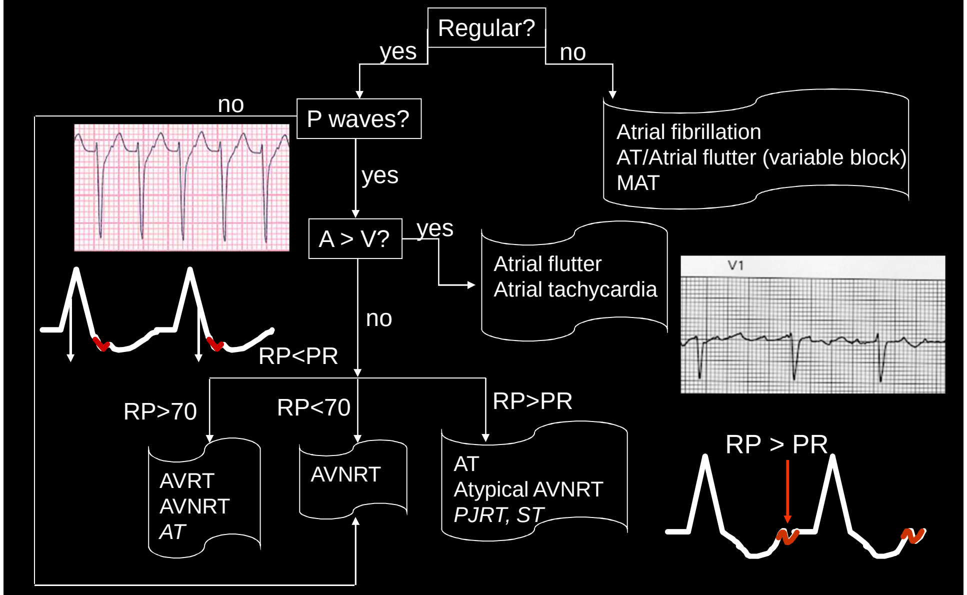
- Hemodynamically unstable → shock!
  - Do not waste time debating the source of a rhythm that needs to be urgently terminated
  - Hypotension, delta MS, CHF, angina – all indicate organ dysfunction requiring rhythm termination
  - Terminate by…
    - Cardioversion if ventricular activity organized
    - Defibrillation (asynchronous) for VF



- Is it narrow (QRS<120 ms)?
  - If yes, odds are that it is SVT
  - VT ***can*** be narrow – in fact, if the arrhythmia QRS is more narrow than the sinus QRS, it likely ***is*** VT
  - If it's wide, it can still be SVT…but it should be assumed to be VT until you can prove to yourself that it is supraventricular

NARROW QRS COMPLEX TACHYCARDIAS

Narrow QRS Tachycardia, Hemodynamically Stable



Regular?

yes

no

Atrial fibrillation
AT/Atrial flutter (variable block)
MAT

P waves?

no

yes

A > V?

yes

Atrial flutter
Atrial tachycardia

no

RP<PR

RP>70

AVRT
AVNRT
AT

RP<70

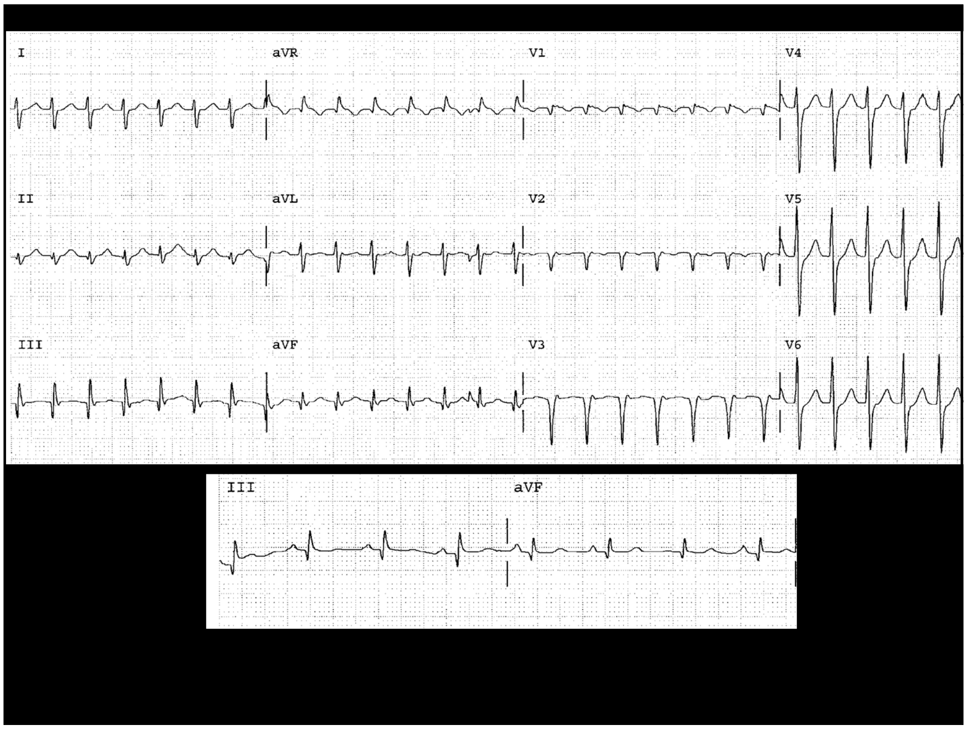
AVNRT

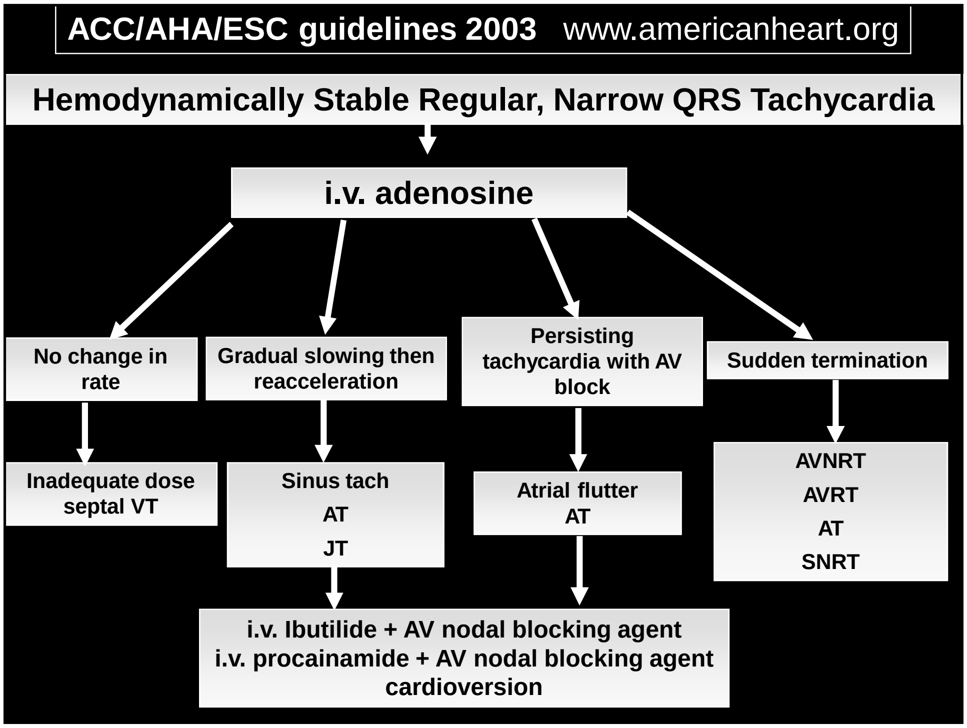
RP>PR

AT
Atypical AVNRT
PJRT, ST

RP > PR

Blomström-Lundqvist and Scheinman ***et al.*** **2003**
ACC/AHA/ESC Practice Guidelines





ACC/AHA/ESC guidelines 2003 www.americanheart.org

Hemodynamically Stable Regular, Narrow QRS Tachycardia

i.v. adenosine

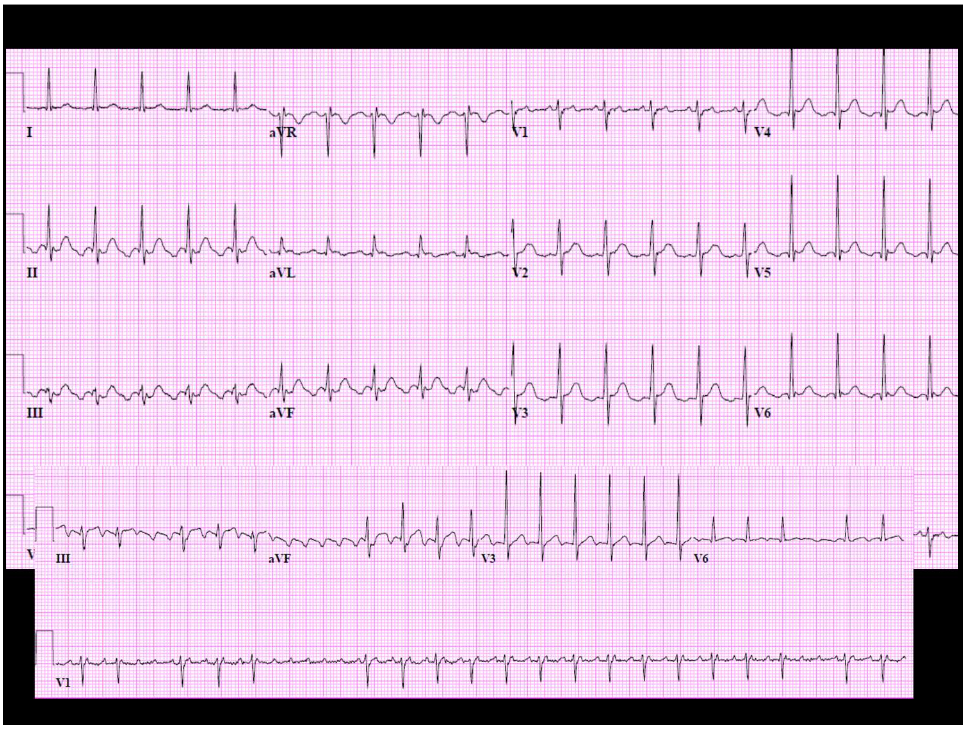
No change in rate
- **Inadequate dose**
- **septal VT**

Gradual slowing then reacceleration
- **Sinus tach**
- **AT**
- **JT**

Persisting tachycardia with AV block
- **Atrial flutter**
- **AT**

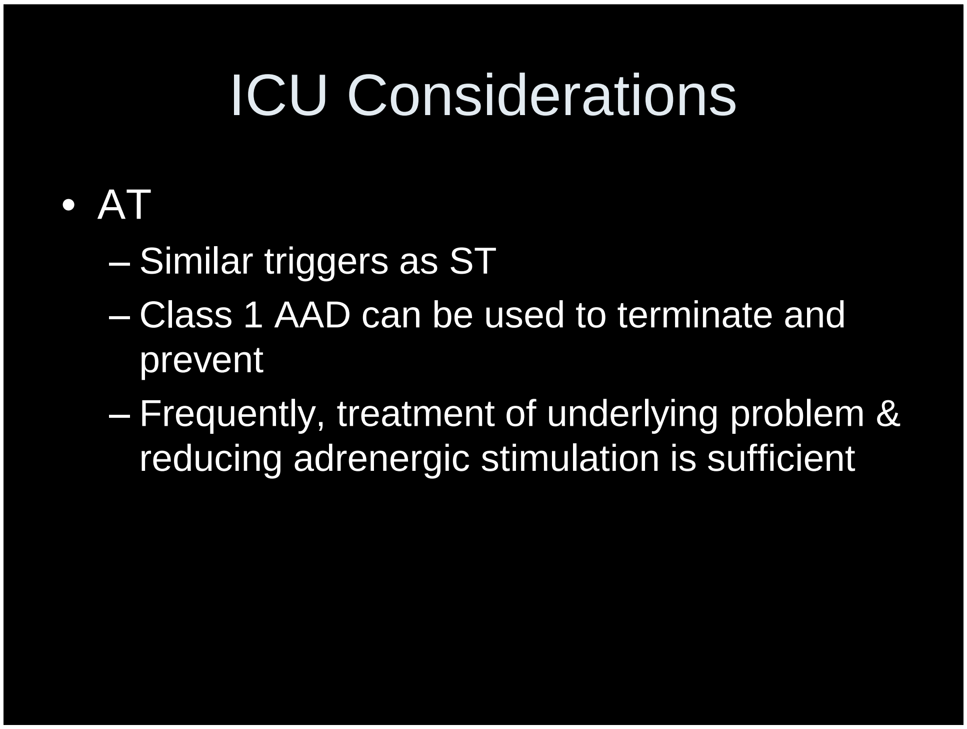
Sudden termination
- **AVNRT**
- **AVRT**
- **AT**
- **SNRT**

i.v. Ibutilide + AV nodal blocking agent
i.v. procainamide + AV nodal blocking agent
cardioversion


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V
III
aVF
V3
V6
V1

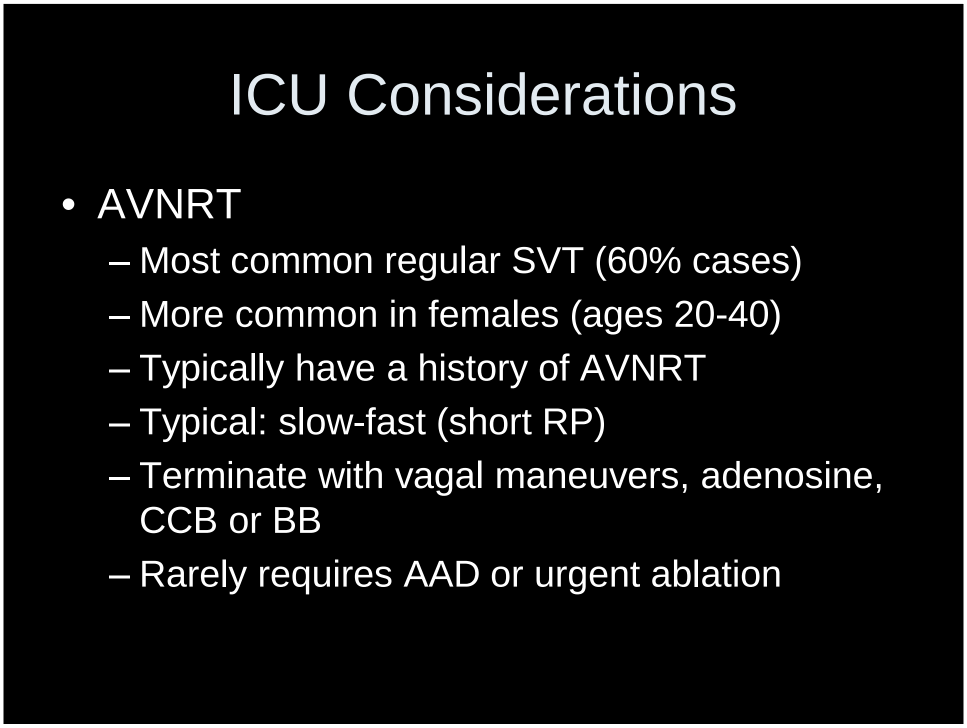
ICU Considerations

- ST
  - Increased automaticity of SN in setting of critical illness; adrenergic medications; hypovolemia, inflammation
  - Gradual increase in rate
  - Treatment geared towards underlying condition
  - Certain situations may warrant rate control (critical CAD, MS, DHF)



ICU Considerations

- AT
  - Similar triggers as ST
  - Class 1 AAD can be used to terminate and prevent
  - Frequently, treatment of underlying problem & reducing adrenergic stimulation is sufficient



ICU Considerations

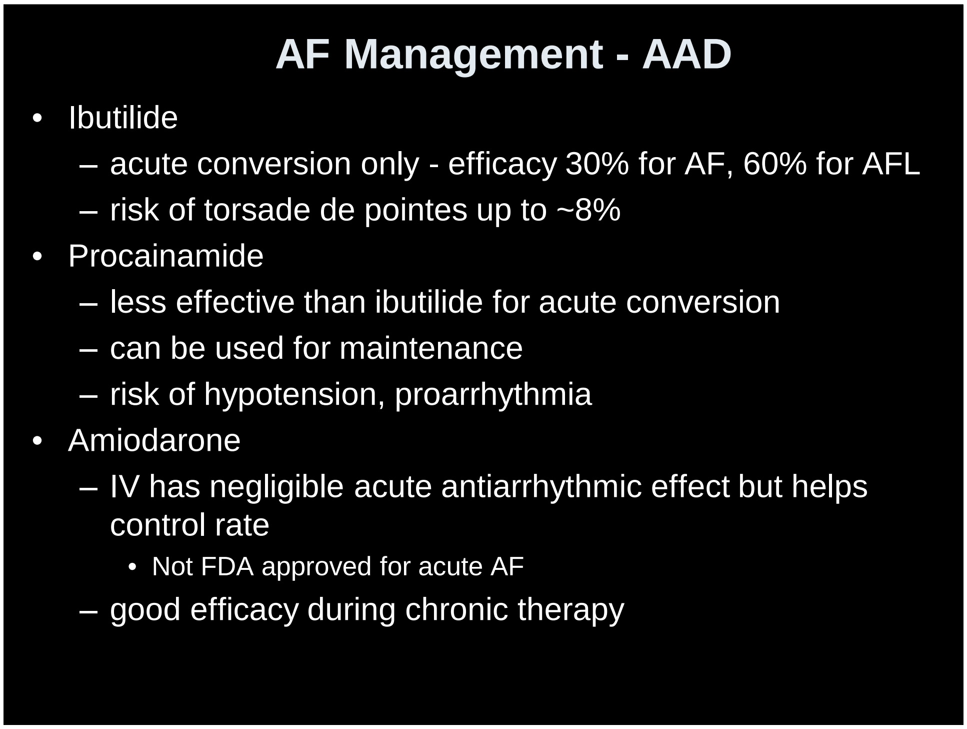
- AVNRT
  - Most common regular SVT (60% cases)
  - More common in females (ages 20-40)
  - Typically have a history of AVNRT
  - Typical: slow-fast (short RP)
  - Terminate with vagal maneuvers, adenosine, CCB or BB
  - Rarely requires AAD or urgent ablation

ICU Considerations

- AVRT
  - Muscular connection between A & V bypassing AVN
  - ORT: antegrade AVN, retrograde AP (NC)
  - ART: antegrade AP, retrograde AVN (WC)
  - Terminate with AVN blockers (adenosine, BB, etc)
  - Preexcited tachycardia: SVT (e.g. AF) bypasses AVN due to AP. In these cases, AVN blockade contraindicated➔procainamide or urgent CV

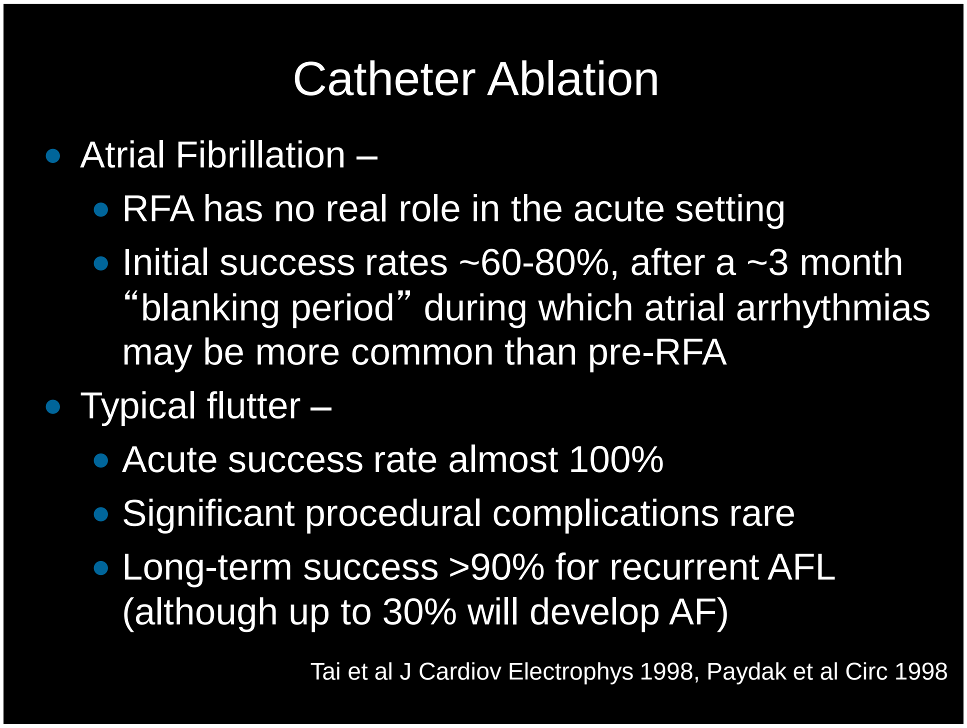
ICU Considerations

- AF
  - Most common type of arrhythmia and most common SVT in ICU
  - May be problematic due to HD instability (rapid ventricular rates, shortened diastolic filling)
  - Another important complication is LA thrombus formation
  - RF: hypertension, MI, LA stretch, pericarditis, myocarditis, valvular heart disease, obesity, metabolic syndrome, PE, alcohol, surgery, OSA, thyrotoxicosis, inflammatory states
  - Rate vs. rhythm control should be individualized



AF Management - AAD

- Ibutilide
  - acute conversion only - efficacy 30% for AF, 60% for AFL
  - risk of torsade de pointes up to ~8%
- Procainamide
  - less effective than ibutilide for acute conversion
  - can be used for maintenance
  - risk of hypotension, proarrhythmia
- Amiodarone
  - IV has negligible acute antiarrhythmic effect but helps control rate
    - Not FDA approved for acute AF
  - good efficacy during chronic therapy



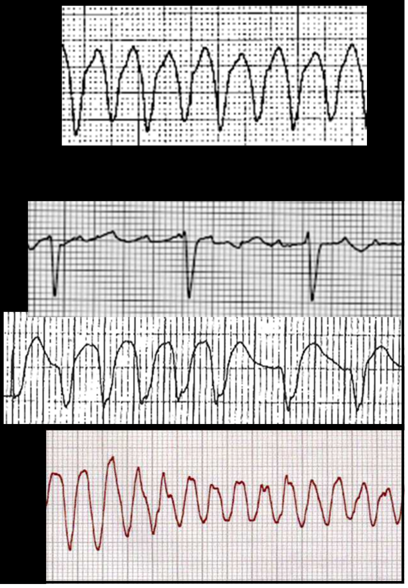
Catheter Ablation

- Atrial Fibrillation –
  - RFA has no real role in the acute setting
  - Initial success rates ~60-80%, after a ~3 month “blanking period” during which atrial arrhythmias may be more common than pre-RFA
- Typical flutter –
  - Acute success rate almost 100%
  - Significant procedural complications rare
  - Long-term success >90% for recurrent AFL (although up to 30% will develop AF)

Tai et al J Cardiov Electrophys 1998, Paydak et al Circ 1998

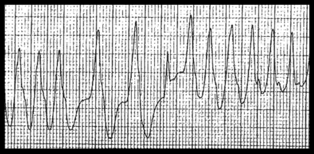
WIDE COMPLEX TACHYCARDIA

Wide Complex Tachycardia

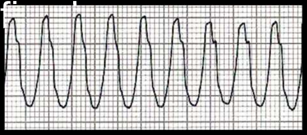


Accessory Pathways in WCT

- AF in WPW – irregular, wide, often with variable morphology
  - cardioversion
  - Ibutilide
  - Procainamide
  - nothing that affects AV node!

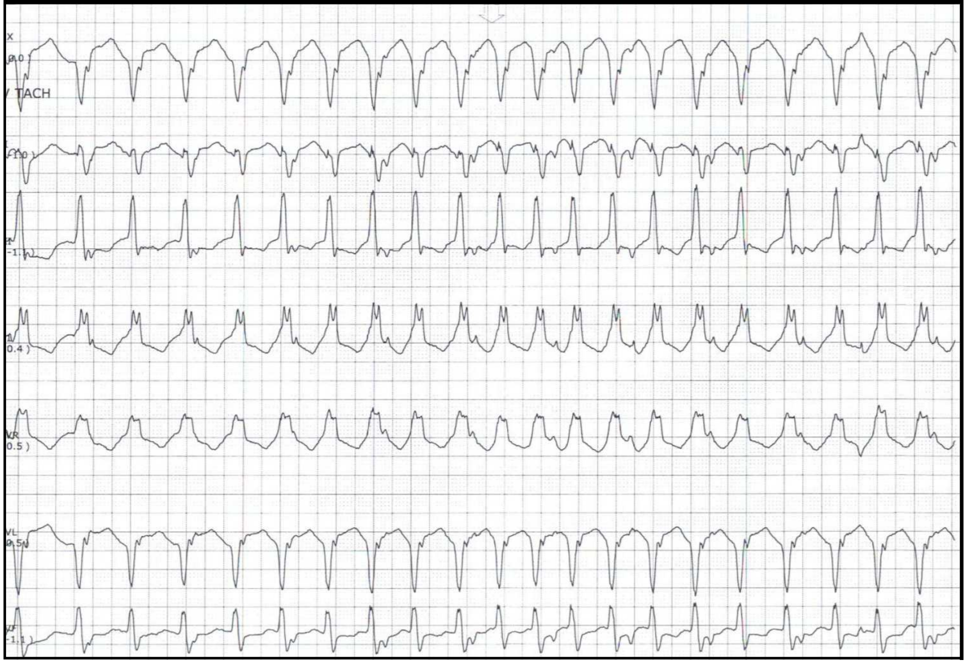


- Antidromic AVRT – regular, wide, f morphology
  - Cardioversion
  - Procainamide
  - *Hemodynamically stable - i.v. adenosine (although, small risk of provoking AF!)*

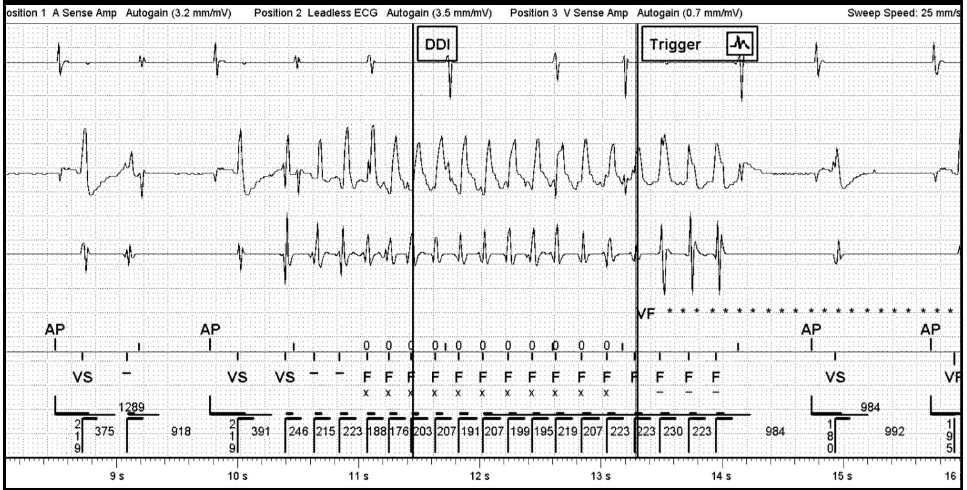


Markers of VT

- Concordance
  - No Q or S in any precordial lead (positive concordance) or no R (QS only) in all precordial leads (negative concordance)
- Intrinsicoid deflection >100 ms
  - Measured from R onset to S nadir
- A-V dissociation where V > A
  - Fusion and Capture beats suggest AV dissociation
- Morphology



AV dissociation (ICD)


Position 1 A Sense Amp Autogain (3.2 mm/mV)
Position 2 Leadless ECG Autogain (3.5 mm/mV)
Position 3 V Sense Amp Autogain (0.7 mm/mV)
Sweep Speed: 25 mm/s
DDI
Trigger
VF
AP
VS
F
1289
375
918
391
246
215
223
188
176
203
207
191
207
199
195
219
207
223
223
230
223
984
984
992
9 s
10 s
11 s
12 s
13 s
14 s
15 s
16

Morphology Criteria favoring VT

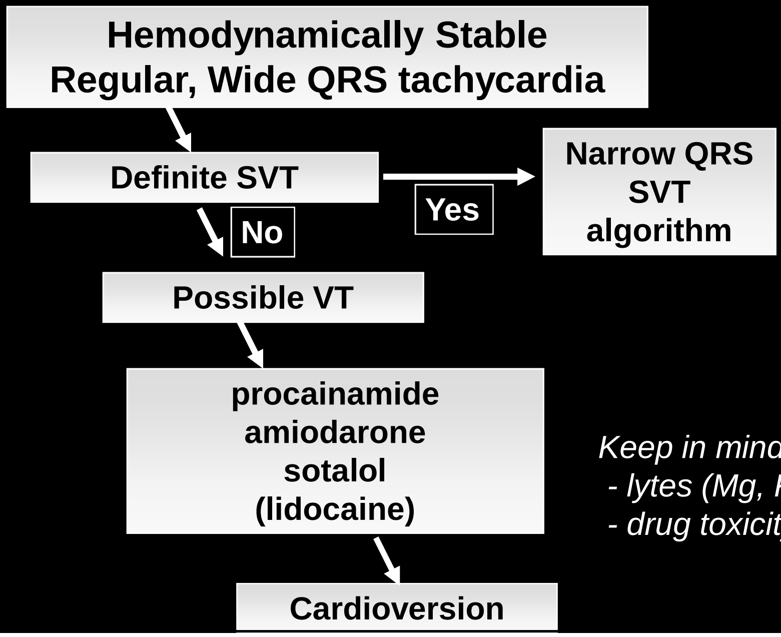
RBBB Pattern

- V1 –
  - monophasic R
  - qR / Rs
- V6
  - S>R
  - QS

LBBB Pattern

- V1/V2 –
  - R>30 ms
  - Intrinsicoid deflection >60 ms
- V6
  - qR or qS

ACC/AHA/ESC guidelines 2010 www.americanheart.org



Hemodynamically Stable Regular, Wide QRS tachycardia

Definite SVT

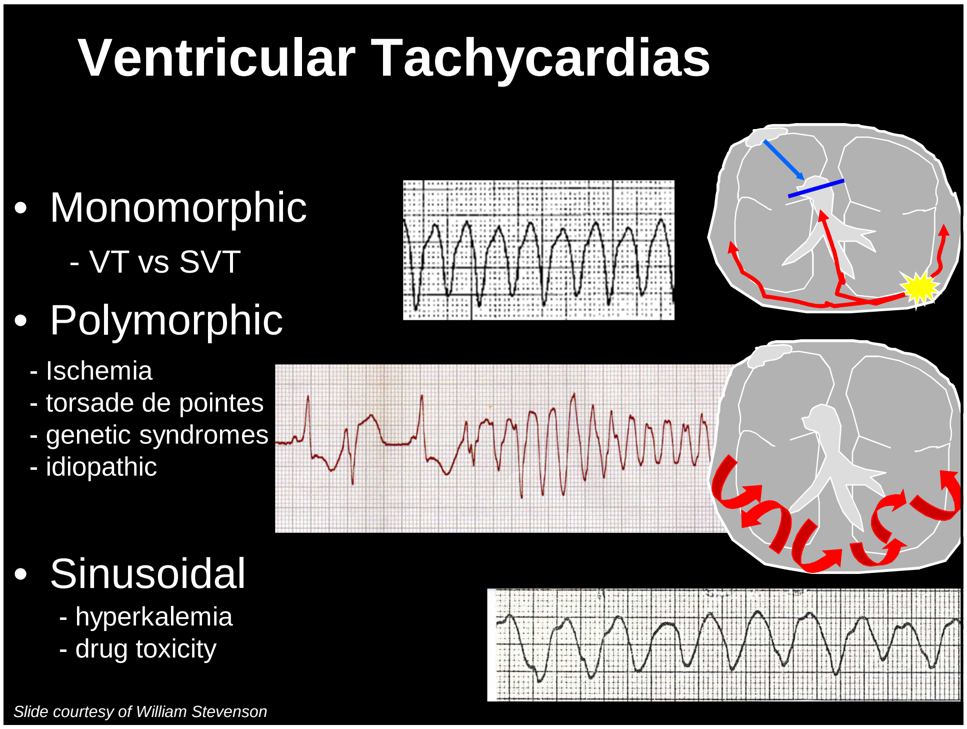
Yes → **Narrow QRS SVT algorithm**

No → **Possible VT**

procainamide
amiodarone
sotalol
(lidocaine)

Cardioversion

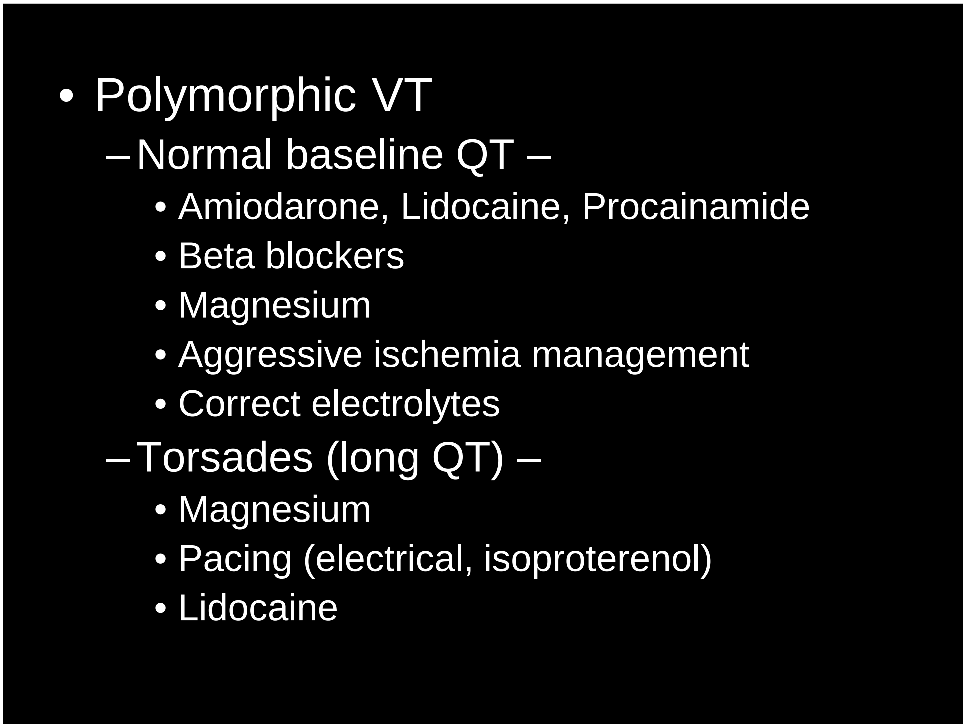
Keep in mind…
- lytes (Mg, K)
- drug toxicity



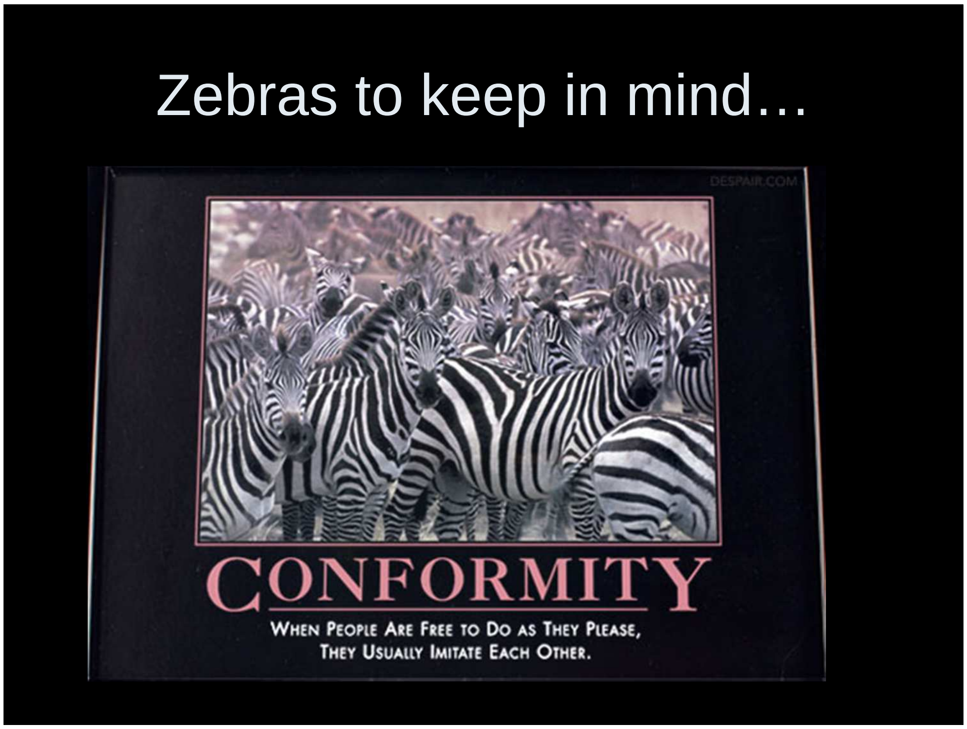
Ventricular Tachycardias

- Monomorphic
  - VT vs SVT
- Polymorphic
  - Ischemia
  - torsade de pointes
  - genetic syndromes
  - idiopathic
- Sinusoidal
  - hyperkalemia
  - drug toxicity

Slide courtesy of William Stevenson

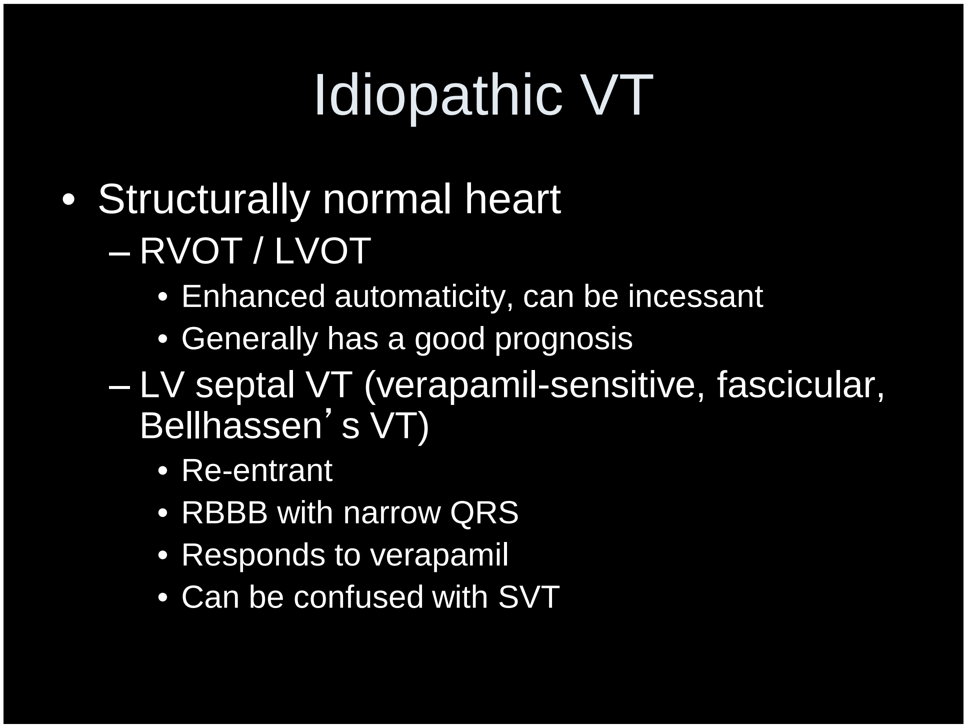


- Polymorphic VT
  - Normal baseline QT –
    - Amiodarone, Lidocaine, Procainamide
    - Beta blockers
    - Magnesium
    - Aggressive ischemia management
    - Correct electrolytes
  - Torsades (long QT) –
    - Magnesium
    - Pacing (electrical, isoproterenol)
    - Lidocaine



Zebras to keep in mind…

DESPAIR.COM
CONFORMITY
WHEN PEOPLE ARE FREE TO DO AS THEY PLEASE, THEY USUALLY IMITATE EACH OTHER.



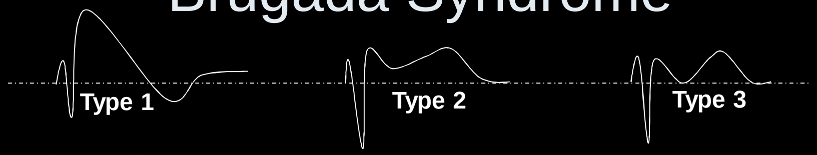
Idiopathic VT

- Structurally normal heart
  - RVOT / LVOT
    - Enhanced automaticity, can be incessant
    - Generally has a good prognosis
  - LV septal VT (verapamil-sensitive, fascicular, Bellhassen’s VT)
    - Re-entrant
    - RBBB with narrow QRS
    - Responds to verapamil
    - Can be confused with SVT

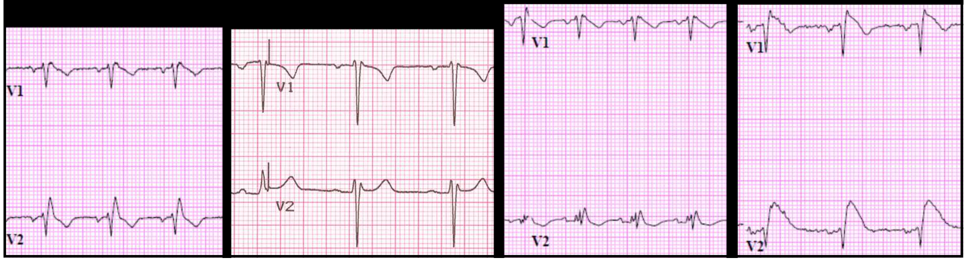
Arrhythmogenic RV Dysplasia (ARVD/C)

- Fatty / fibrous replacement of myocardium, classically in RV although LV can be affected
- Ventricular arrhythmias frequently observed
- ECG: can have suggestive features but can be normal
  - up to 85% T-wave inversion in V1 - V3
  - RBBB in ~20%
  - Epsilon wave in ~30%

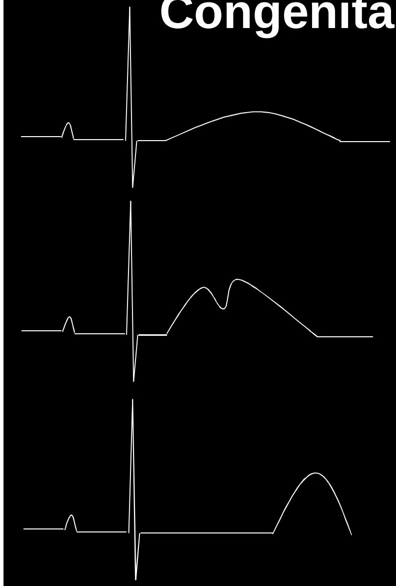
Brugada Syndrome



Type 1	Type 2	Type 3
“Coved” ST	Saddleback ST	Saddleback ST
Negative T wave	Positive / Biphasic T	Positive T
ST terminal segment gradually descending	ST terminal segment elevated ≥1 mm	ST terminal segment elevated <1 mm



Congenital Long QT Syndrome

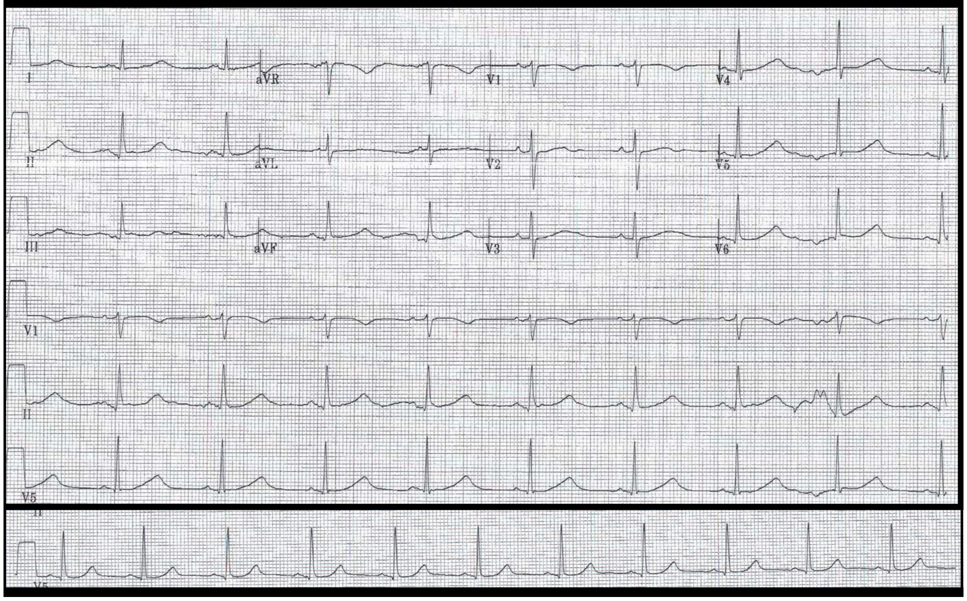


LQT1 –
- potassium channel mutation
- SCD associated with swimming
- beta blocker significantly protective

LQT2 –
- potassium channel mutation
- SCD associated with emotional episodes, sound stimuli (alarm clock)
- beta blocker decreases risk

LQT3 –
- sodium channel mutation
- SCD associated with sleep
- beta blockers of unclear/limited benefit

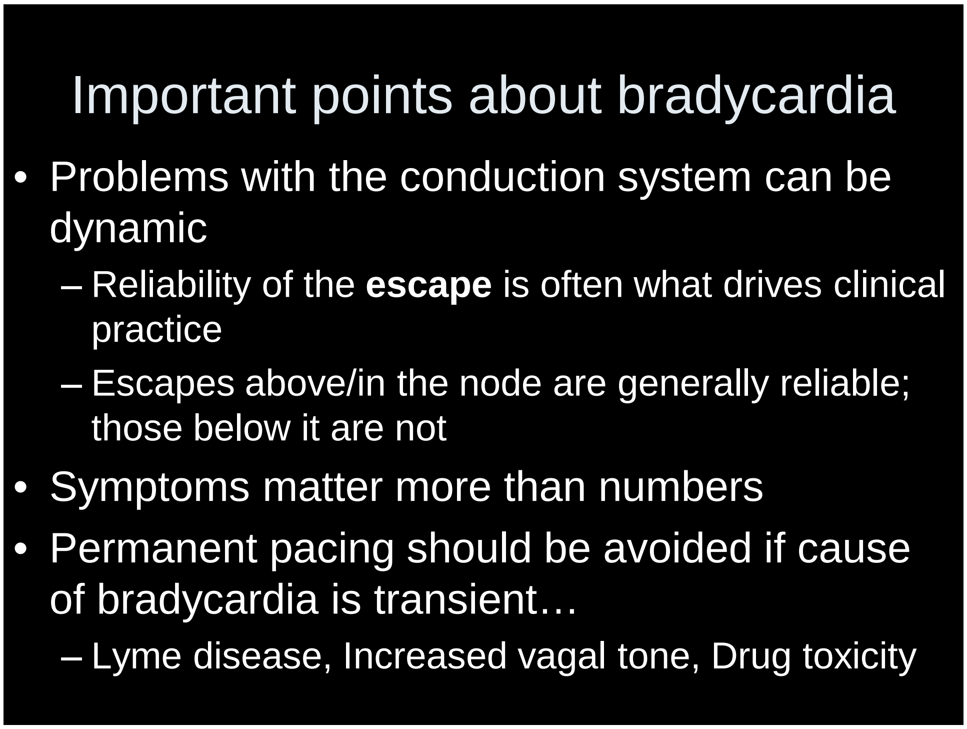
Drug-induced long QT



BRADYARRHYTHMIAS

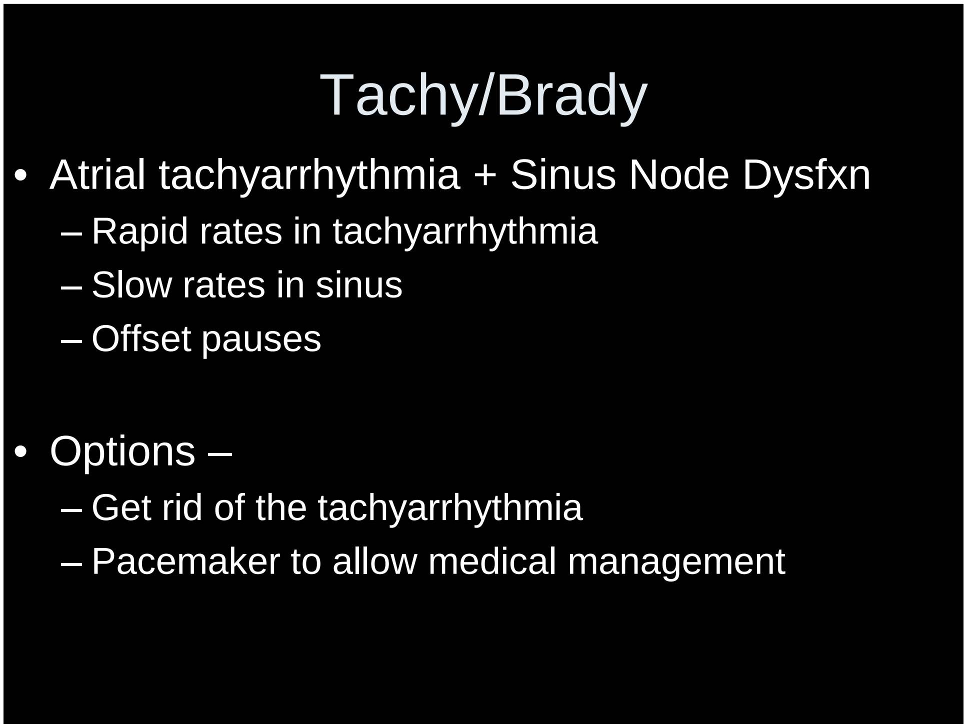
Bradyarrhythmias

- Sinus node
  - Sinus bradycardia
  - Sinus node exit block
  - Sinus arrest / sinus dysfunction
- AV node
- His/Purkinje system
  - If conduction block is below AV node, atropine will *not* help you



Important points about bradycardia

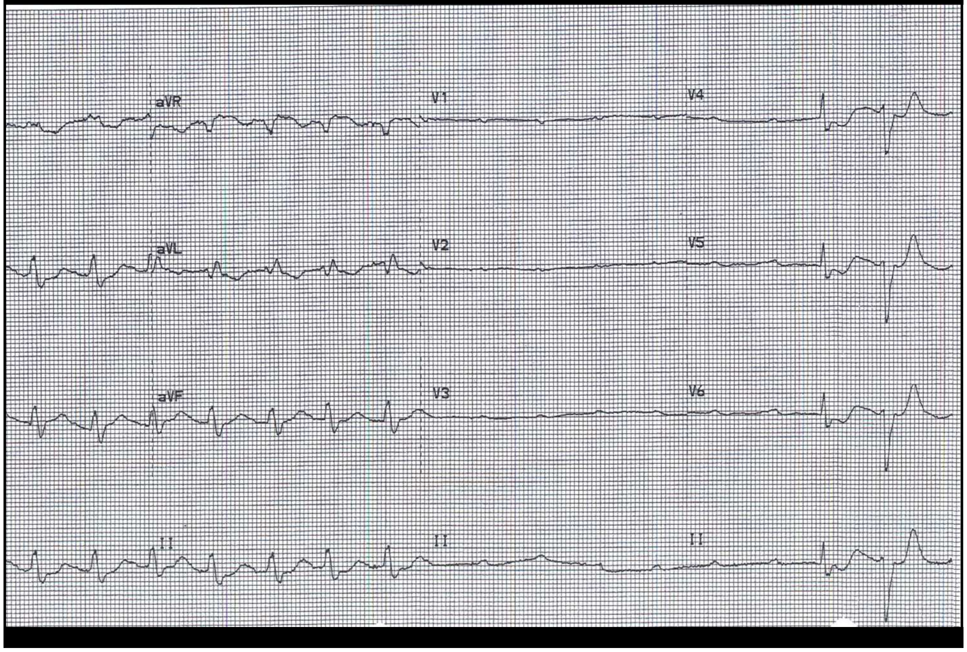
- Problems with the conduction system can be dynamic
  - Reliability of the **escape** is often what drives clinical practice
  - Escapes above/in the node are generally reliable; those below it are not
- Symptoms matter more than numbers
- Permanent pacing should be avoided if cause of bradycardia is transient…
  - Lyme disease, Increased vagal tone, Drug toxicity



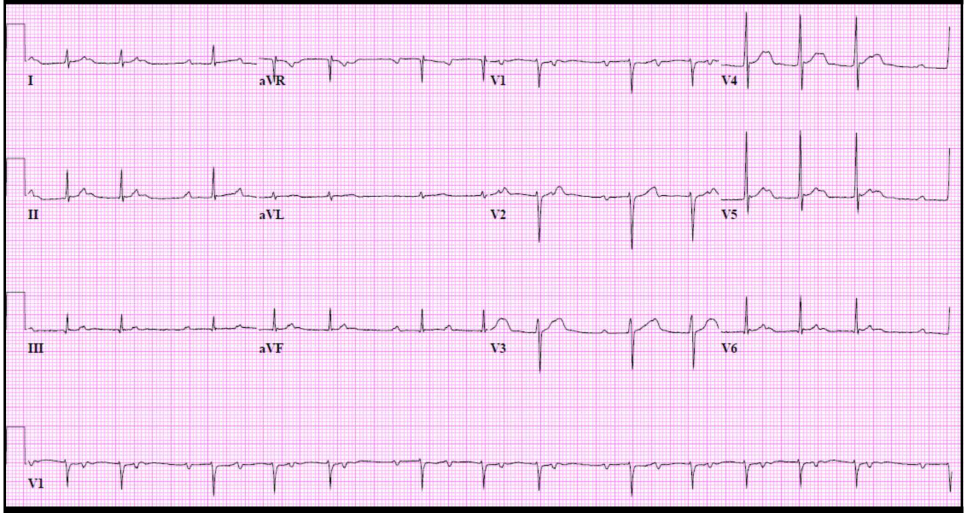
Tachy/Brady

- Atrial tachyarrhythmia + Sinus Node Dysfxn
  - Rapid rates in tachyarrhythmia
  - Slow rates in sinus
  - Offset pauses

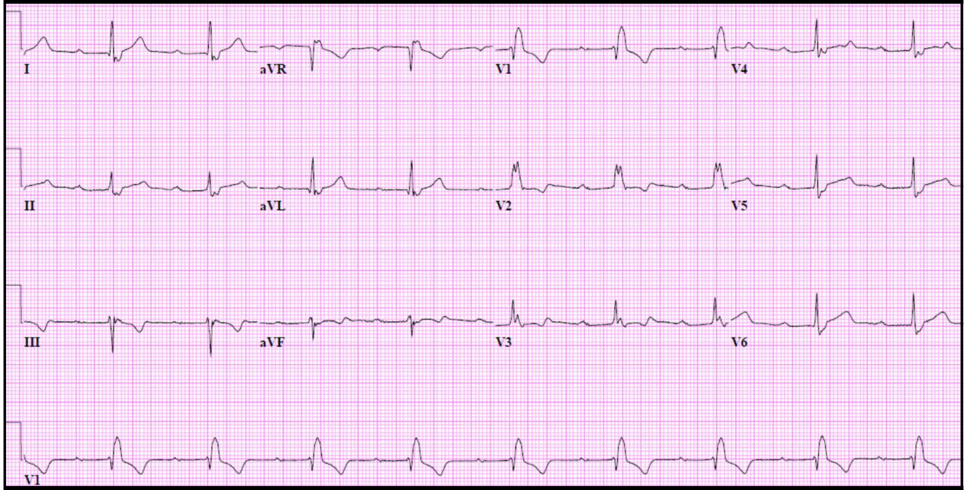
- Options –
  - Get rid of the tachyarrhythmia
  - Pacemaker to allow medical management


aVR
V1
V4
aVL
V2
V5
aVF
V3
V6
II
II
II

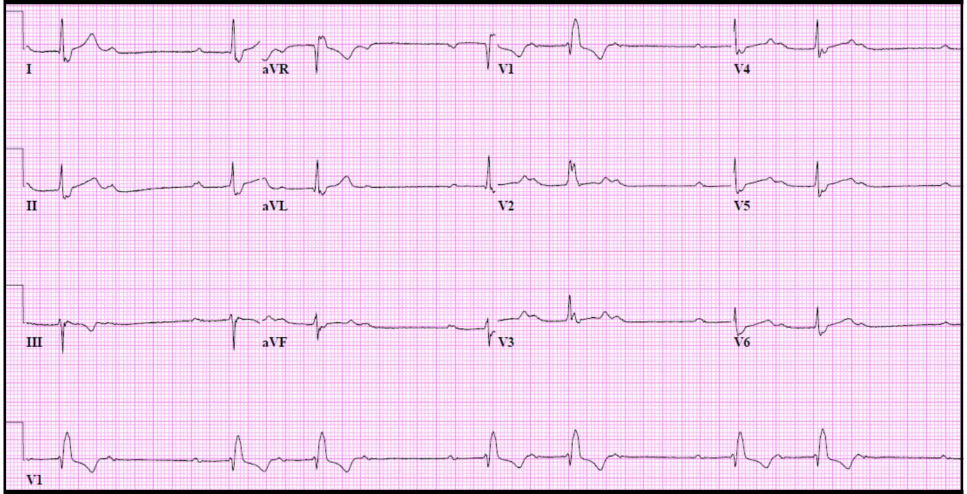
Mobitz I – PR lengthens, RR shortens
- typical of AV nodal block
- benign prognosis


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

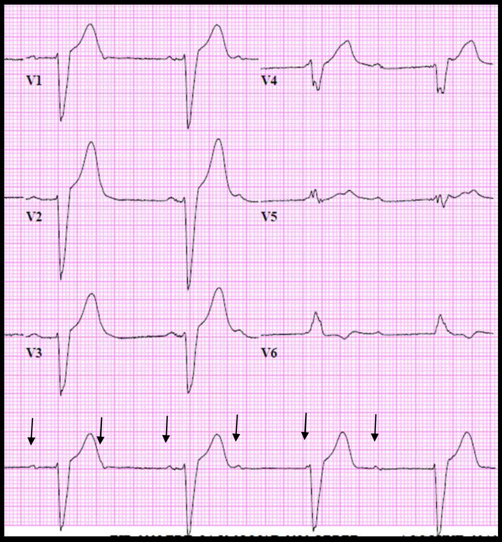
“Trifascicular block”


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

Mobitz I…


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

With CHB!



Take Home Points

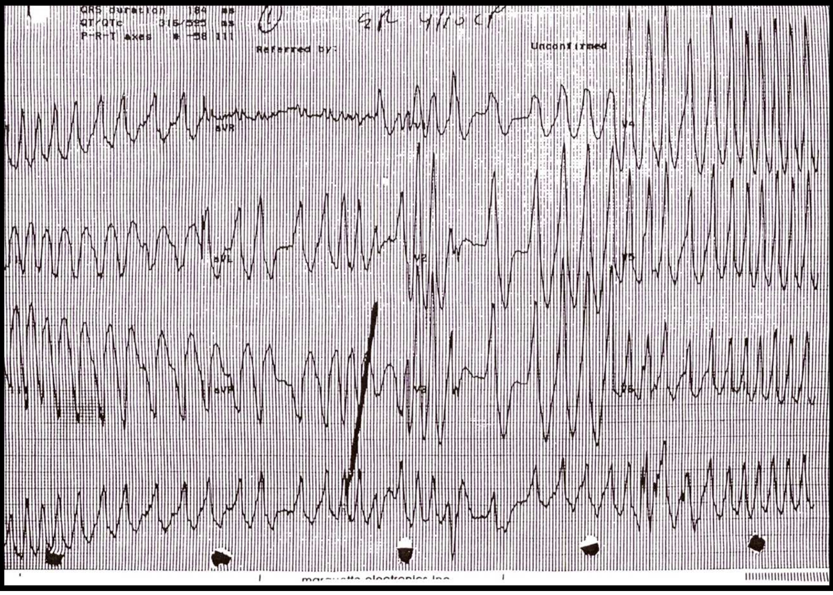
- Hemodynamic instability = shock
- WCT – assume VT until proven otherwise
- SVT – vagal manuevers / adenosine to diagnose and treat unless you have WPW – with WPW, no nodal agents/interventions (proc!)
- Heritable arrhythmic disorders – you won't see them unless you think of them!
- Bradyarrhythmias – symptoms and reliability of escape drive management

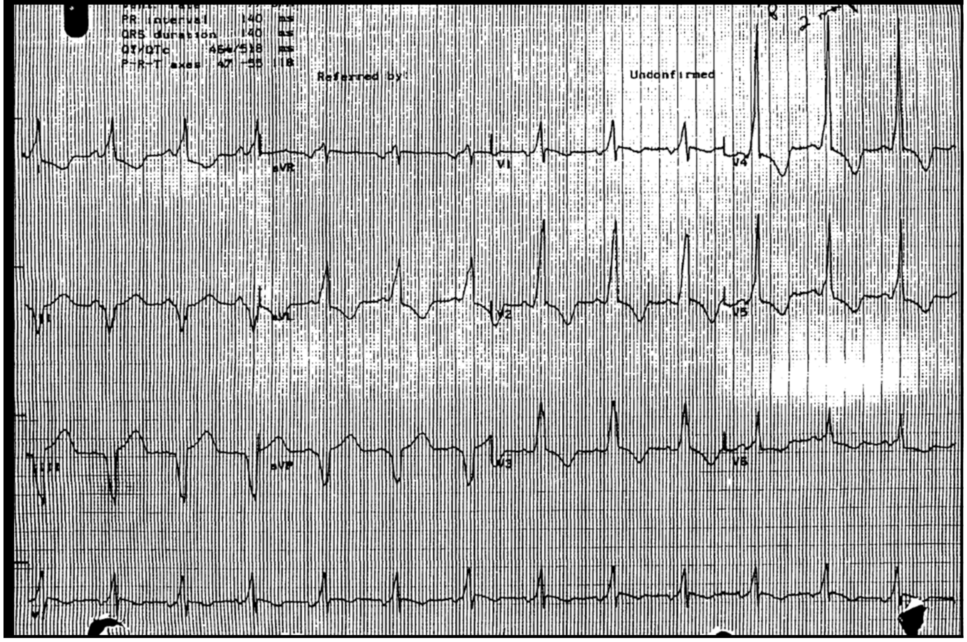
References

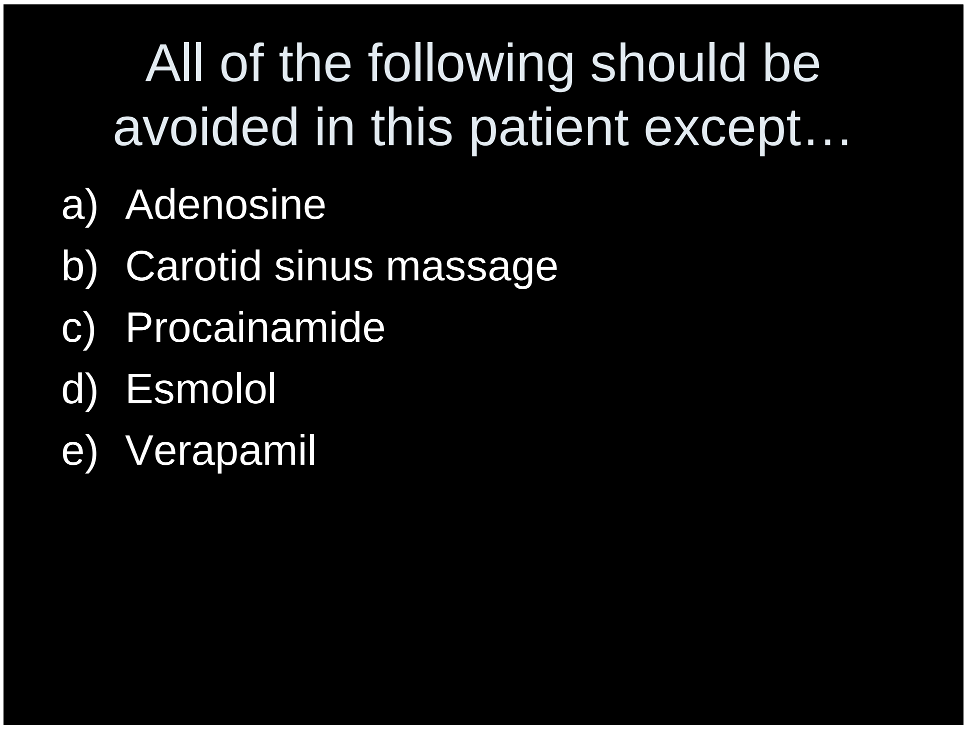
- ACC/AHA/ESC Guidelines for the management of patients with supraventricular arrhythmias. Blomström-Lundqvist et al., J Am Coll Cardiol 2003;42:1493–531.
- ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death – Executive summary. Zipes DP et al., Circulation 2006, 114:1088-1132.
- A practical guide for clinicians who treat patients with amiodarone. Goldschlager et al., Heart Rhythm 2007, 4:1250-1259.
- ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: Executive summary. Epstein AE et al., Circulation, 2008, 117:2820-2840.

Questions

Question #1

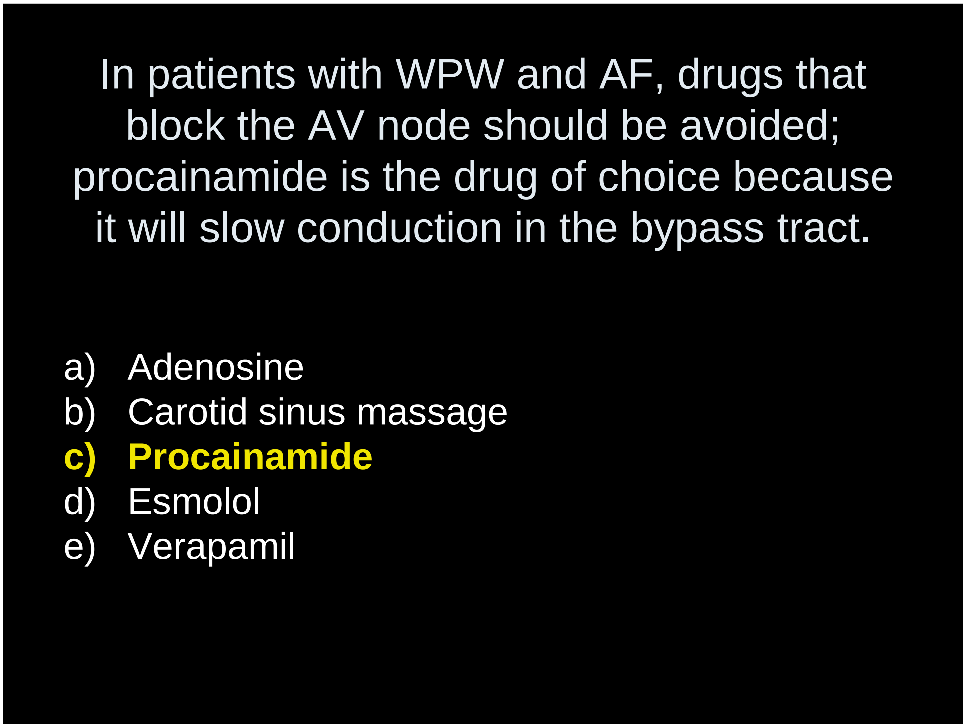

QRS duration 184 ms
QT/QTc 316/525 ms
P-R-T axes * -58 111
Referred by:
Unconfirmed
aVR
V4
aVL
V2
V5
aVF
V3
V6
marquette electronics inc


PR interval 140 ms
QRS duration 140 ms
QT/QTc 464/518 ms
P-R-T axes 47 -55 118
Referred by:
Unconfirmed
aVR
V1
V4
aVL
V2
V5
aVF
V3
V6



All of the following should be avoided in this patient except…

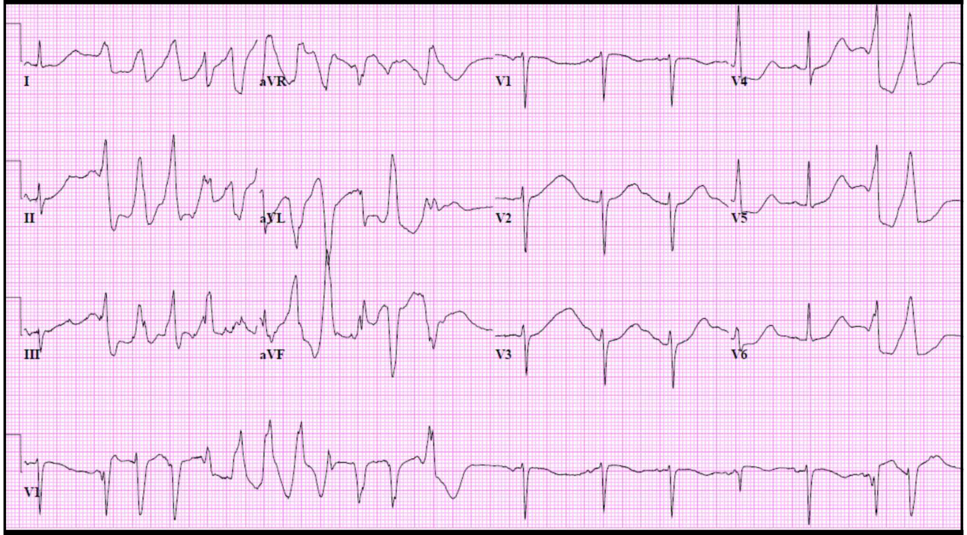
a) Adenosine
b) Carotid sinus massage
c) Procainamide
d) Esmolol
e) Verapamil



In patients with WPW and AF, drugs that block the AV node should be avoided; procainamide is the drug of choice because it will slow conduction in the bypass tract.

a) Adenosine
b) Carotid sinus massage
c) Procainamide
d) Esmolol
e) Verapamil

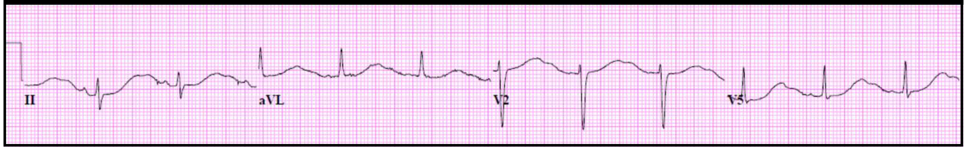
Question #2

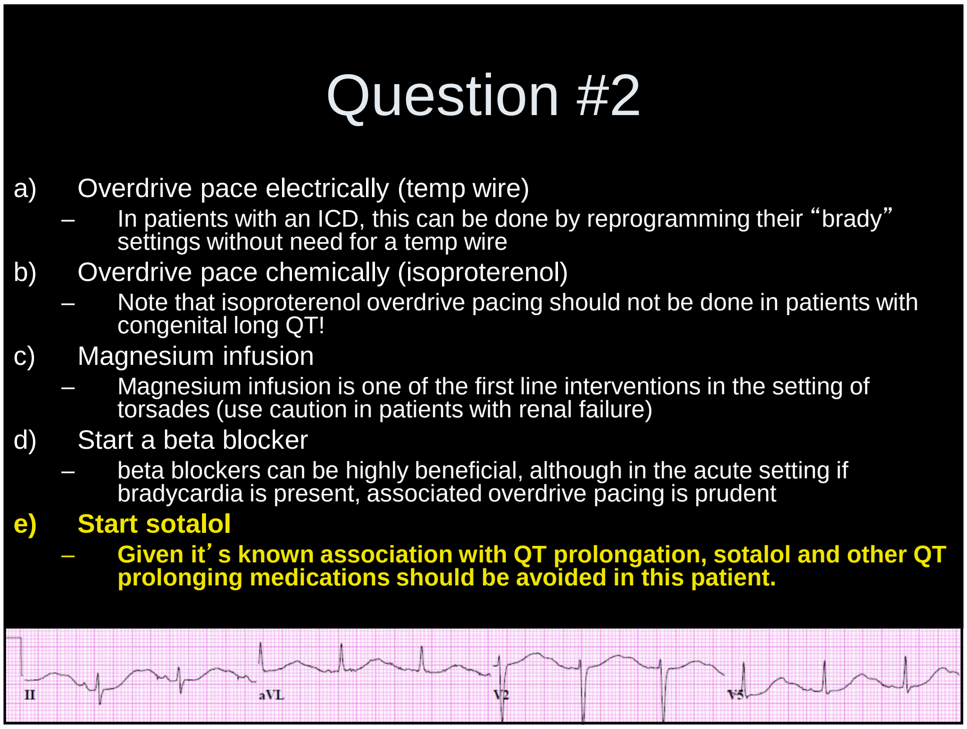

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

Question #2

If the patient's arrhythmia is drug-associated, possible treatments include all of the following except:

a) Overdrive pace electrically (temp wire)
b) Overdrive pace chemically (isoproterenol)
c) Magnesium infusion
d) Start a beta blocker
e) Start sotalol





Question #2

a) Overdrive pace electrically (temp wire)
  - – In patients with an ICD, this can be done by reprogramming their “brady” settings without need for a temp wire

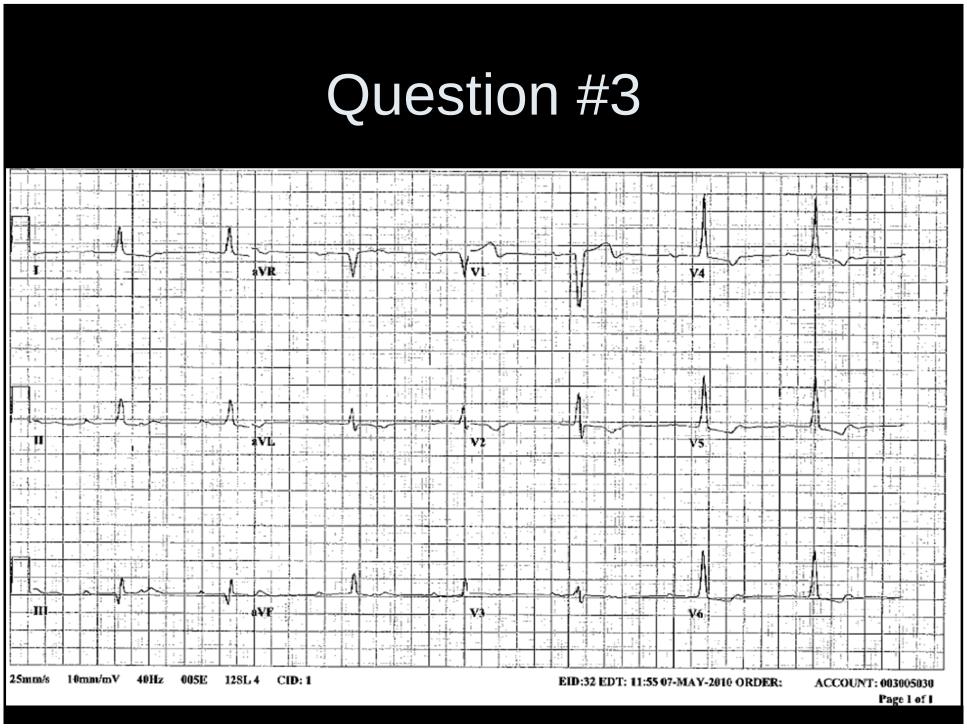
b) Overdrive pace chemically (isoproterenol)
  - – Note that isoproterenol overdrive pacing should not be done in patients with congenital long QT!

c) Magnesium infusion
  - – Magnesium infusion is one of the first line interventions in the setting of torsades (use caution in patients with renal failure)

d) Start a beta blocker
  - – beta blockers can be highly beneficial, although in the acute setting if bradycardia is present, associated overdrive pacing is prudent

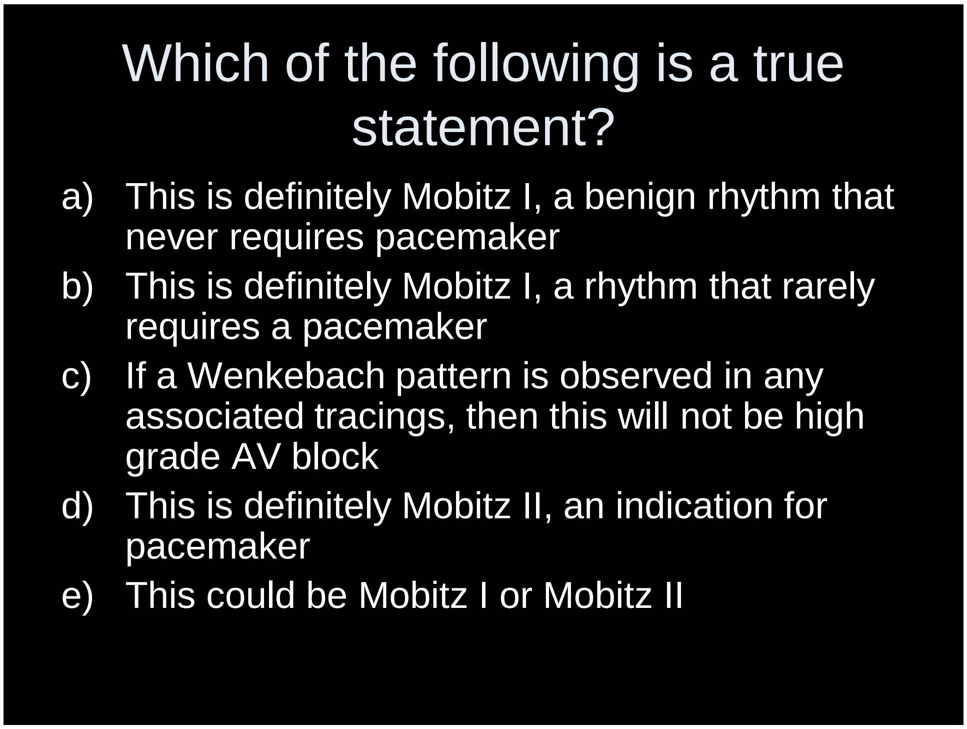
e) Start sotalol
  - – **Given it’s known association with QT prolongation, sotalol and other QT prolonging medications should be avoided in this patient.**

II
aVL
V2
V5



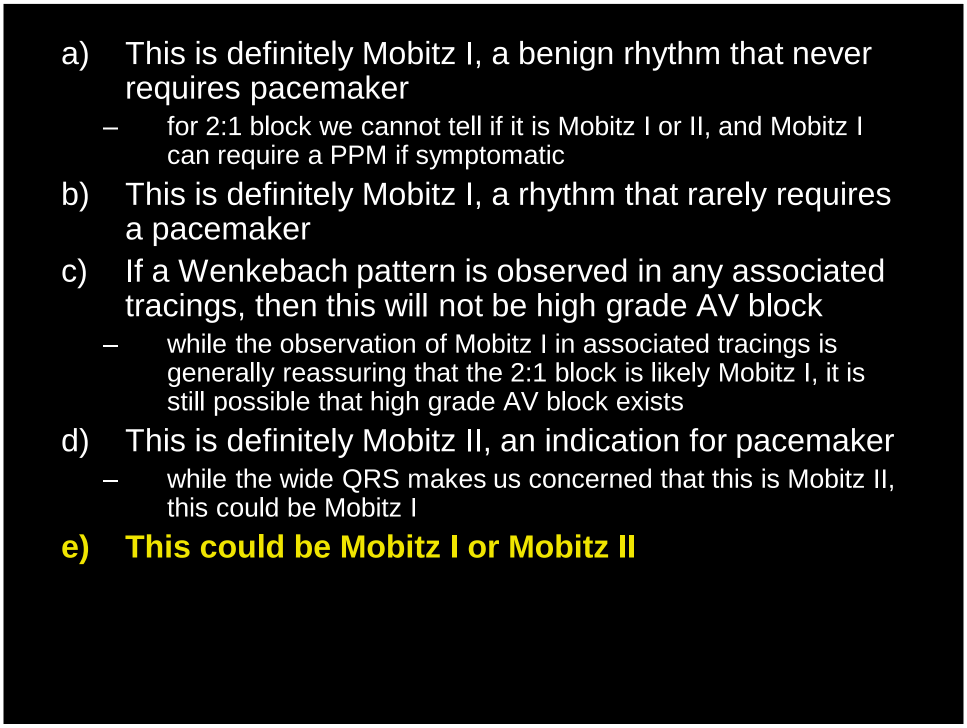
Question #3

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
25mm/s 10mm/mV 40Hz 005E 12SL 4 CID: 1
EID:32 EDT: 11:55 07-MAY-2010 ORDER:
ACCOUNT: 003005030
Page 1 of 1



Which of the following is a true statement?

a) This is definitely Mobitz I, a benign rhythm that never requires pacemaker
b) This is definitely Mobitz I, a rhythm that rarely requires a pacemaker
c) If a Wenkebach pattern is observed in any associated tracings, then this will not be high grade AV block
d) This is definitely Mobitz II, an indication for pacemaker
e) This could be Mobitz I or Mobitz II



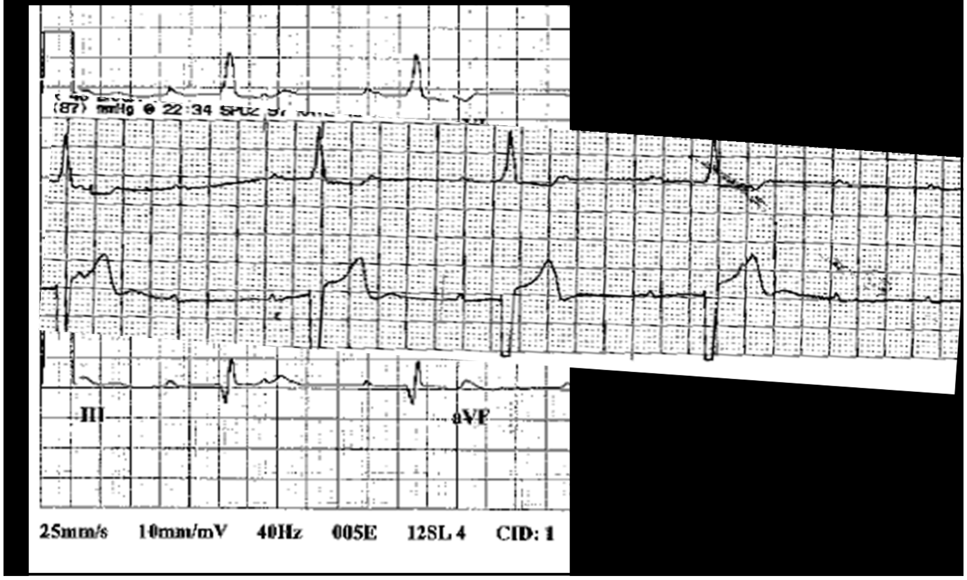
a) This is definitely Mobitz I, a benign rhythm that never requires pacemaker
  - for 2:1 block we cannot tell if it is Mobitz I or II, and Mobitz I can require a PPM if symptomatic

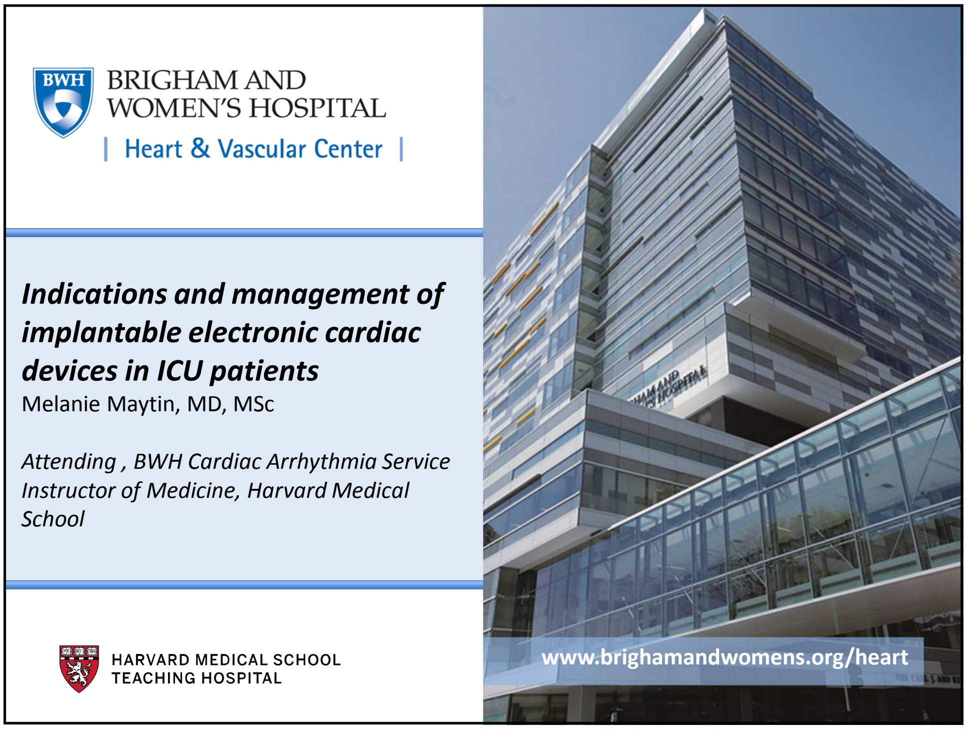
b) This is definitely Mobitz I, a rhythm that rarely requires a pacemaker
c) If a Wenkebach pattern is observed in any associated tracings, then this will not be high grade AV block
  - while the observation of Mobitz I in associated tracings is generally reassuring that the 2:1 block is likely Mobitz I, it is still possible that high grade AV block exists

d) This is definitely Mobitz II, an indication for pacemaker
  - while the wide QRS makes us concerned that this is Mobitz II, this could be Mobitz I

e) This could be Mobitz I or Mobitz II

Question #3


(87) mmHg @ 22:34 SPO2 97
III
aVF
25mm/s 10mm/mV 40Hz 005E 12SL 4 CID: 1



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Indications and management of implantable electronic cardiac devices in ICU patients

Melanie Maytin, MD, MSc

Attending , BWH Cardiac Arrhythmia Service
Instructor of Medicine, Harvard Medical School

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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- Disclosures:
  - Consultant: Medtronic, Spectranetics, St. Jude Medical, Biotronik
  - Research Grants: Spectranetics

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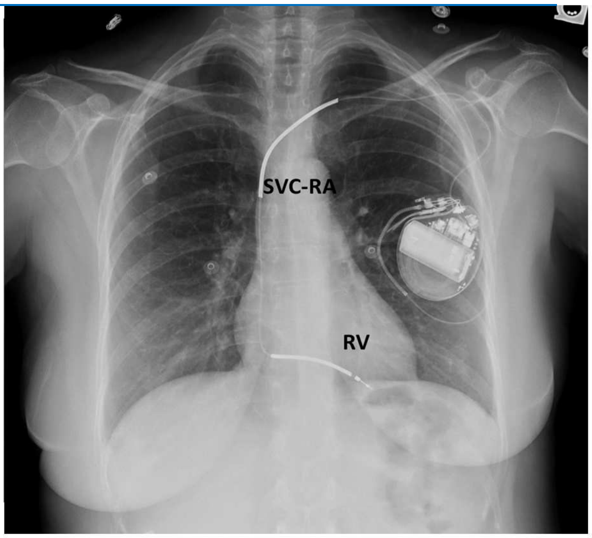
Types of Implantable Cardiac Devices

- Pacemakers
  - Single chamber
  - Dual chamber
- Implantable Cardiac Defibrillators
  - Single chamber
  - Dual chamber
- Cardiac Resynchronization Therapy
  - CRT-D
  - CRT-P



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Types of Implantable Cardiac Devices

- Pacemakers
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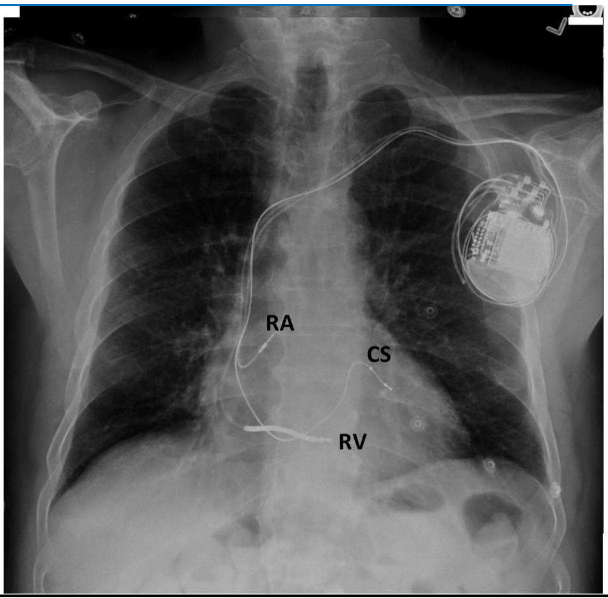
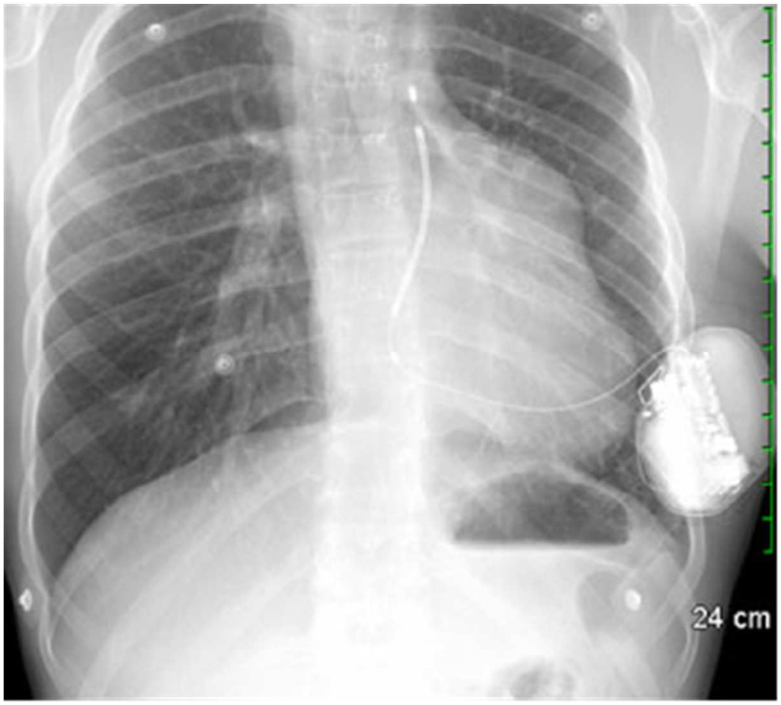
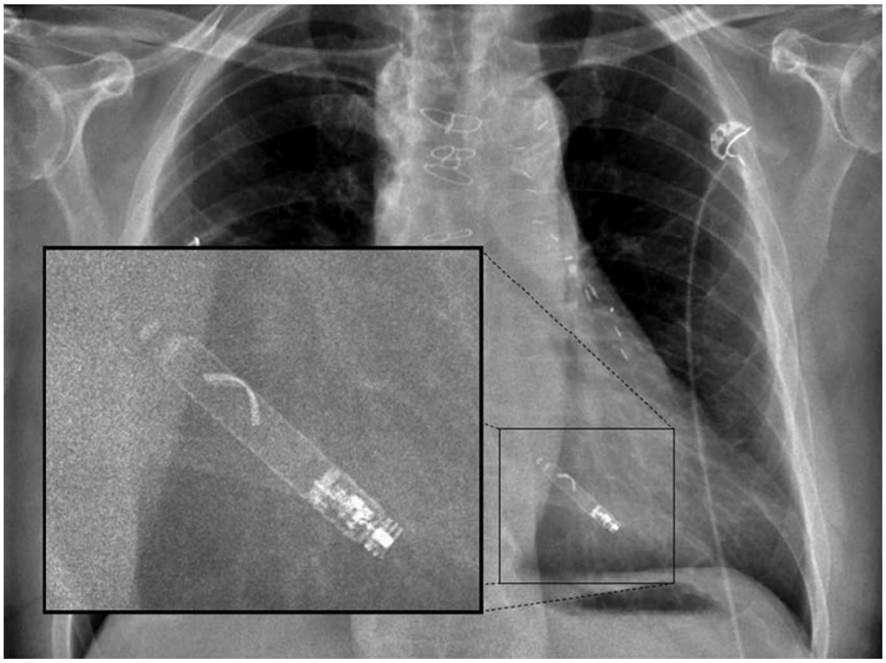
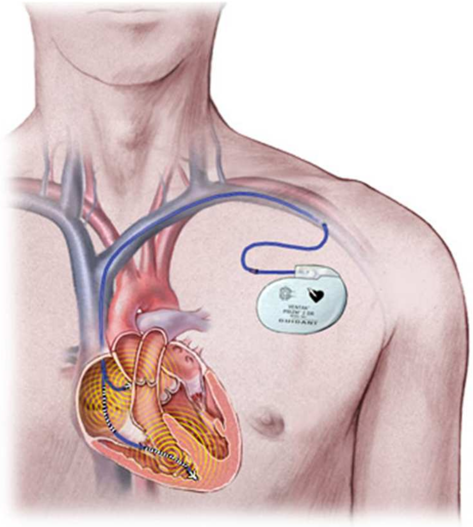
  - CRT-P




24 cm



What Is A Pacemaker?

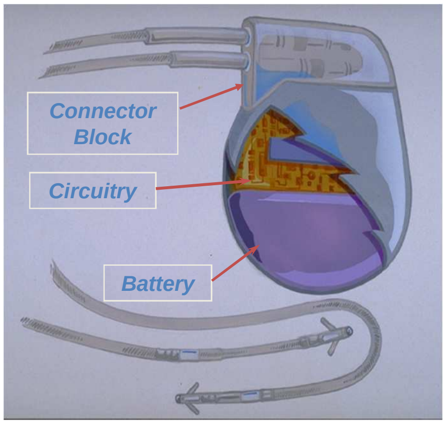


What Pacemakers Do

- Electronic pacemakers deliver electrical impulses that depolarize the myocardial cells near the lead tip, such that the signal propagates into the contiguous myocardium
- Pulses can be delivered in many ways, depending on how the pacemaker is programmed

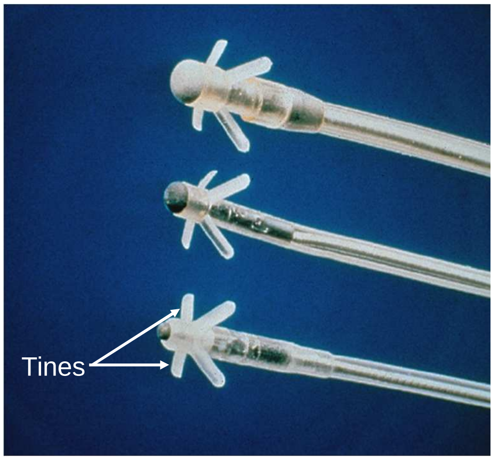
The Pulse Generator

- Contains a battery to provide energy for sending electrical impulses to the heart
- Houses the circuitry that controls pacemaker operations
- Includes a connector to join the pulse generator to the lead(s)



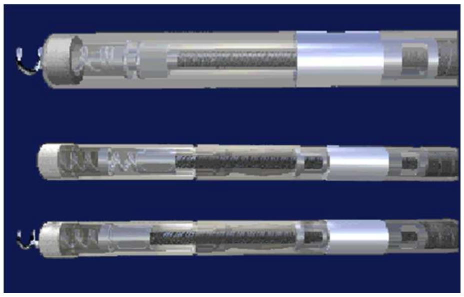
Endocardial Passive Fixation Leads

- The tines become lodged in the trabeculae, a fibrous meshwork, of the heart
- Inserted via a cut-down or transvenous sheath



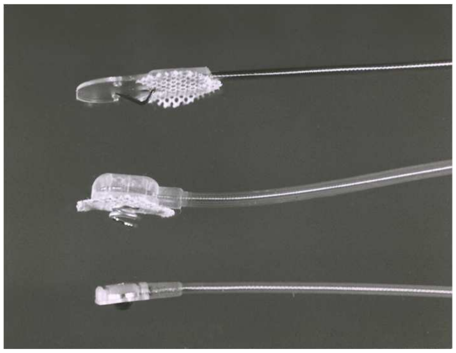
Transvenous Active Fixation Leads

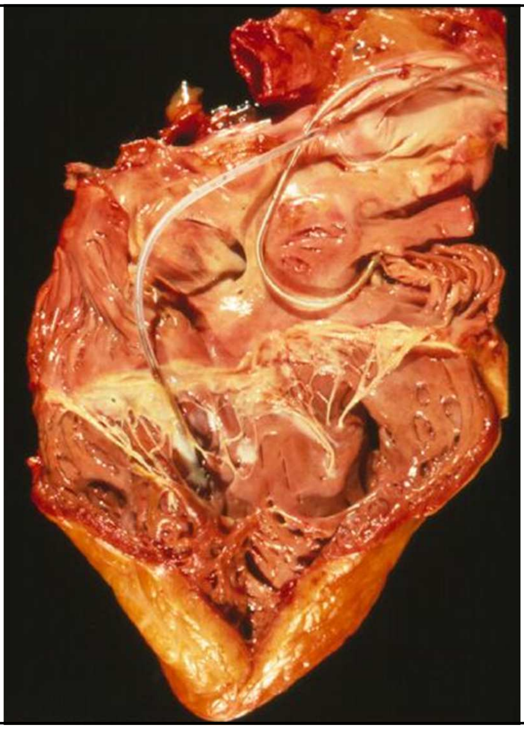
- The helix, or screw, extends into the endocardial tissue
  - Allows for lead positioning anywhere in the heart's chamber
  - The helix is extended using an included tool
  - Inserted via a cut-down or transvenous sheath



Epicardial Leads

- Leads applied directly to the surface of the heart
  - Fixation mechanisms include:
    - Epicardial stab-in
    - Myocardial screw-in
    - Suture-on
  - Applied via sternotomy or laproscopy





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Types of Pacemakers

- Lead in the right atrium
- Lead in the right ventricle
- Leads in both RA and RV
- Leads in RV, LV = biventricular pacer

The NASPE/BPEG generic (NBG) code

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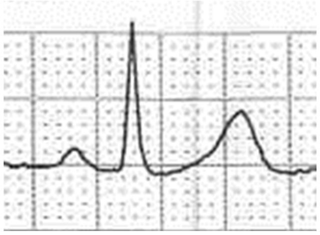
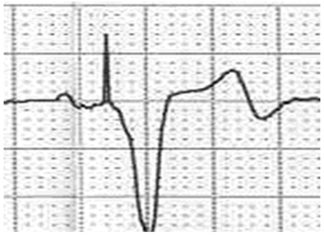
The NASPE/BPEG Generic (NBG) Code

Position	I	II	III	IV	V
Category	Chamber(s) Paced	Chamber(s) Sensed	Response to Sensing	Programmability, rate modulation	Antitachy-arrhythmia Function(s)
Letters Used	O-None A-Atrium V-Ventricle D-Dual (A+V)	O-None A-Atrium V-Ventricle D-Dual (A+V)	O-None T-Triggered I-Inhibited D-Dual (T+I)	O-None P-Simple Programmable M-Multi-Programmable C-Communicating R-Rate modulation	O-None P-Pacing (antitachy-arrhythmia) S-Shock D-Dual (P+S)
Manufac-turer's Designation Only	S- Single (A or V)	S- Single (A or V)			

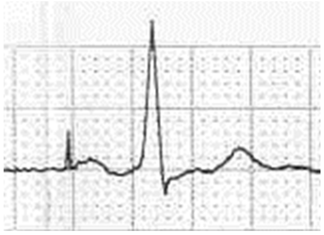
AS VS



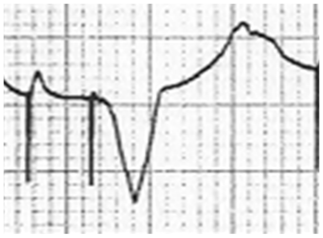
AS VP

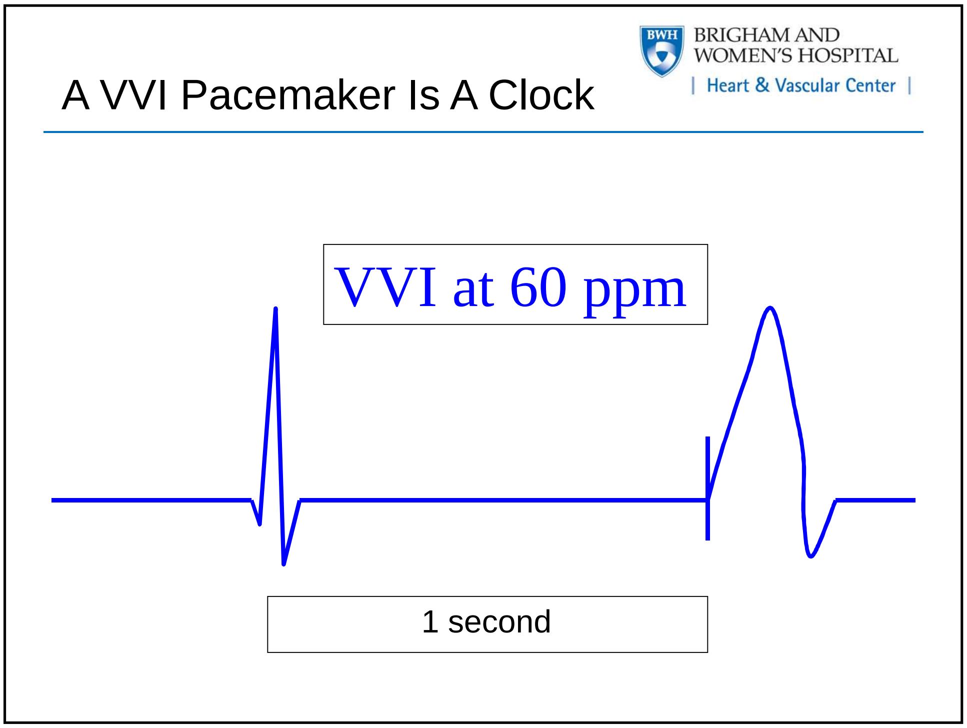


AP VS



AP VP





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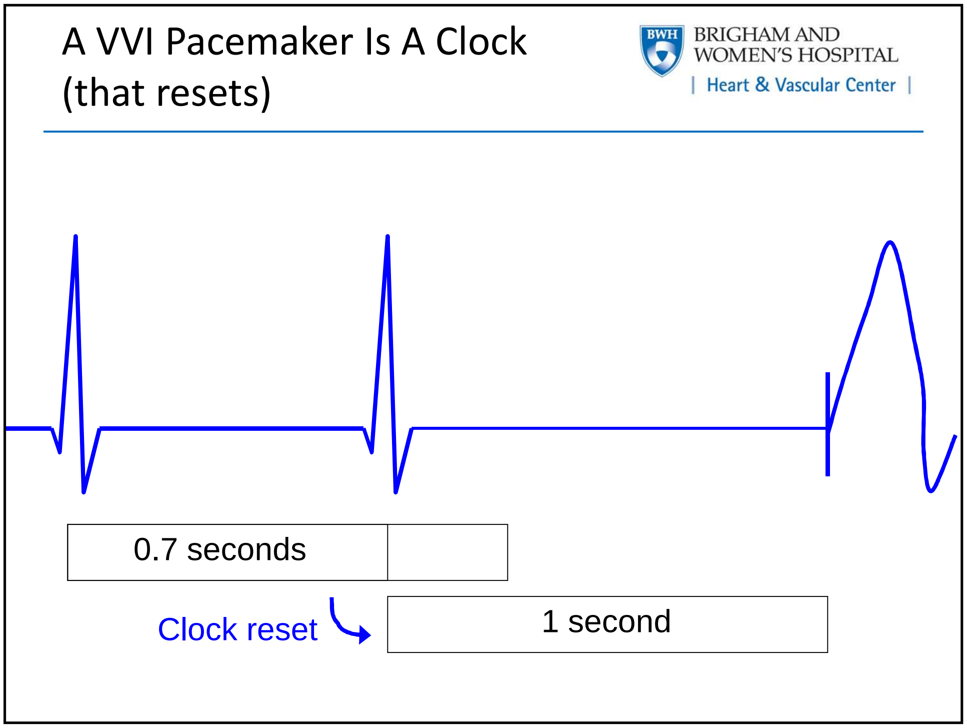
A VVI Pacemaker Is A Clock

VVI at 60 ppm

1 second



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A VVI Pacemaker Is A Clock (that resets)

0.7 seconds

Clock reset

1 second

A DDD Pacemaker is 2 Clocks

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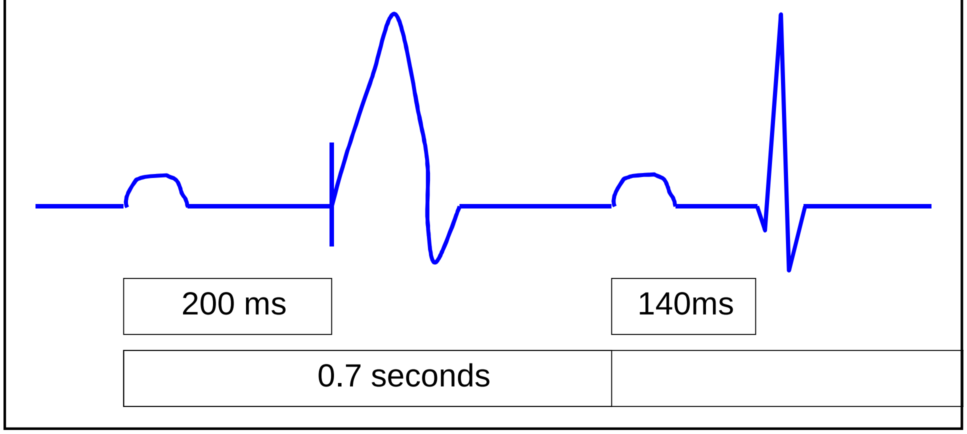
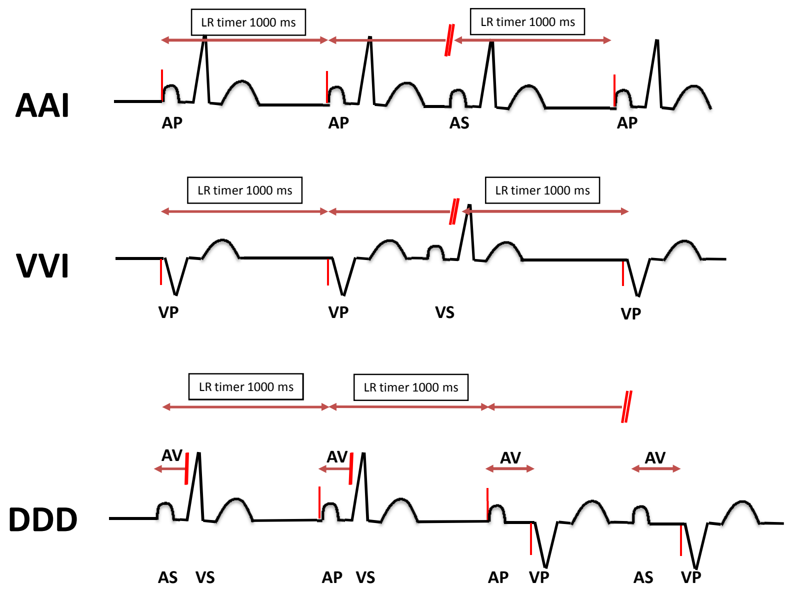
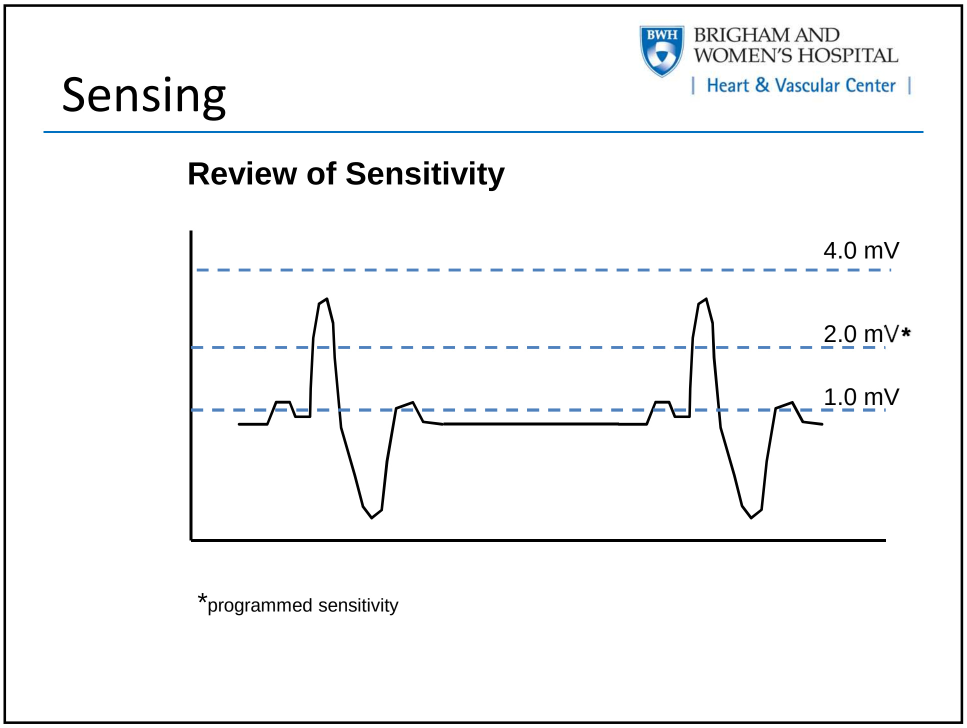
DDD at 60 ppm = rate clock

AV delay 200ms = PR interval clock


200 ms
140ms
0.7 seconds


LR timer 1000 ms
LR timer 1000 ms
AAI
AP
AP
AS
AP
LR timer 1000 ms
LR timer 1000 ms
VVI
VP
VP
VS
VP
LR timer 1000 ms
LR timer 1000 ms
AV
AV
AV
AV
DDD
AS
VS
AP
VS
AP
VP
AS
VP



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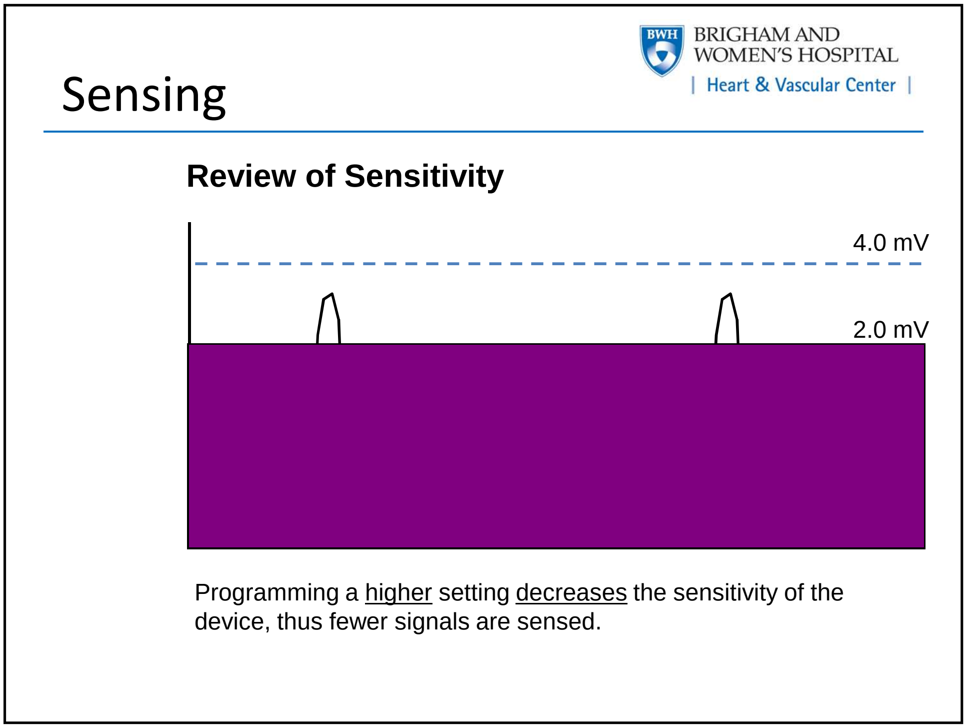
Sensing

Review of Sensitivity

*programmed sensitivity



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Sensing

Review of Sensitivity

Programming a higher setting decreases the sensitivity of the device, thus fewer signals are sensed.

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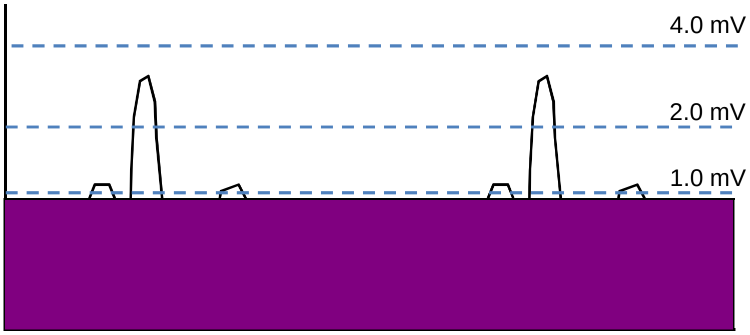
Sensing

Review of Sensitivity



Programming a **lower** setting **increases** the sensitivity of the device, thus more signals are sensed.

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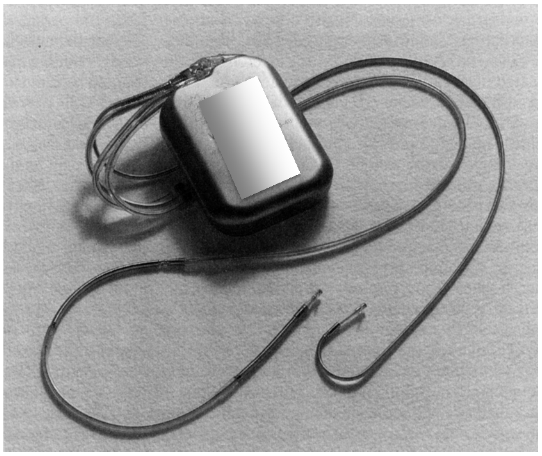
Implantable Defibrillator



ICD Evolution

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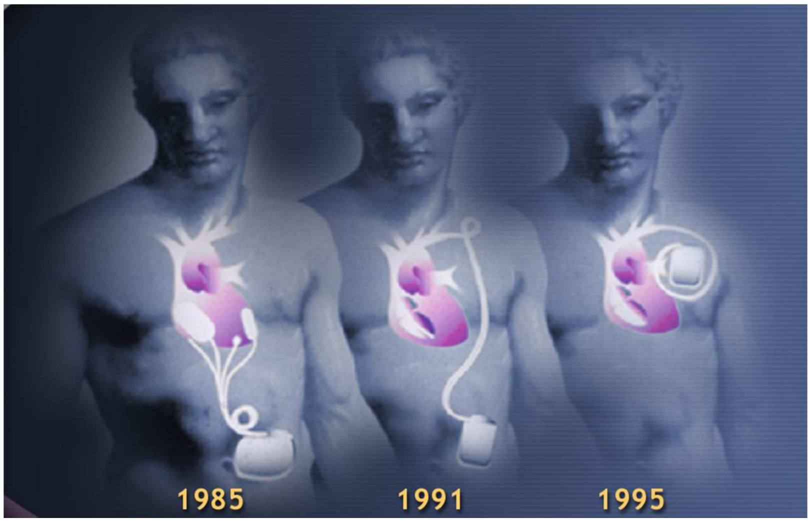
1985
1991
1995

Evolution of ICD Technology

ICD Evolution

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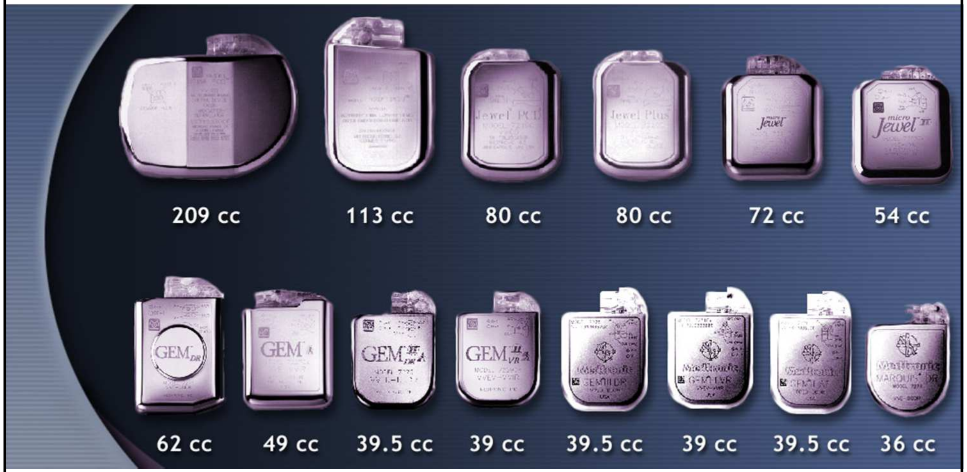
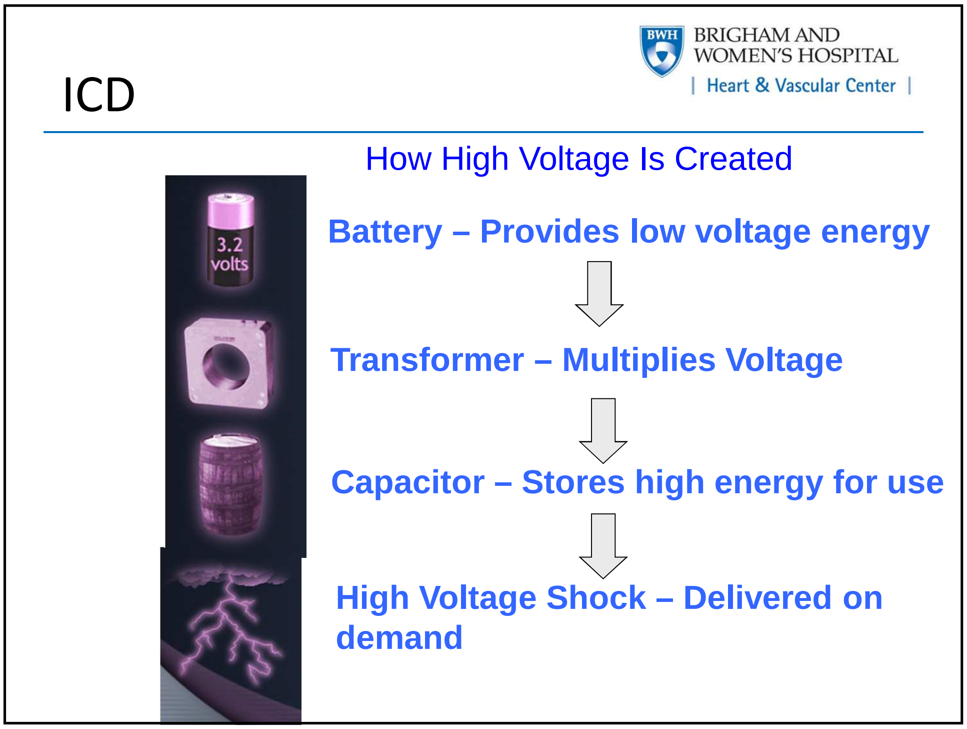

209 cc
113 cc
80 cc
80 cc
72 cc
54 cc
62 cc
49 cc
39.5 cc
39 cc
39.5 cc
39 cc
39.5 cc
36 cc



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ICD

How High Voltage Is Created

Battery – Provides low voltage energy

⇩

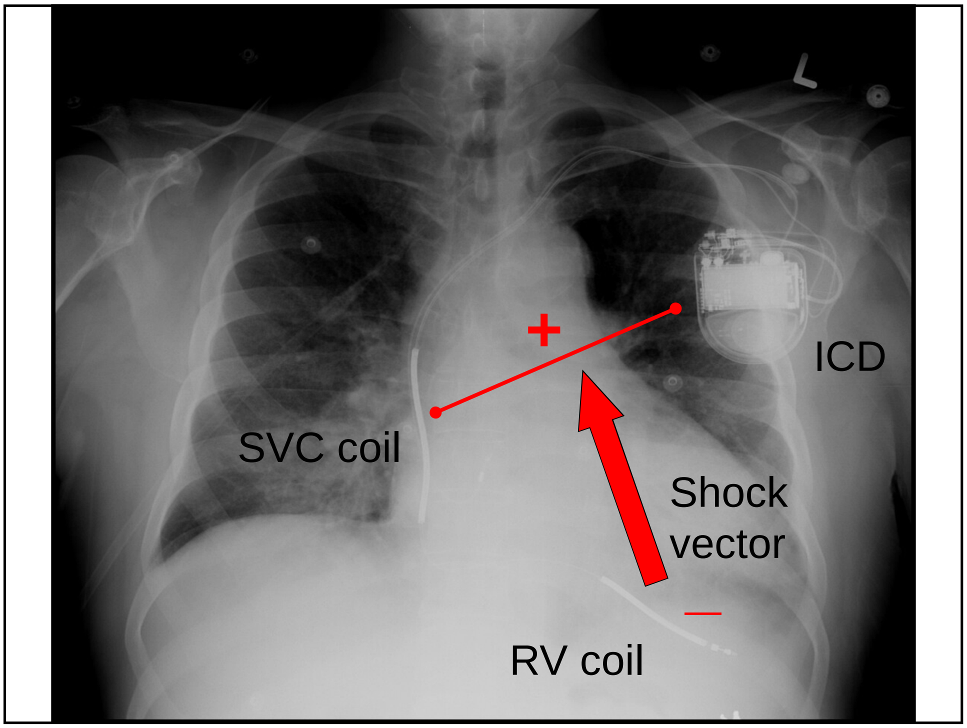
Transformer – Multiplies Voltage

⇩

Capacitor – Stores high energy for use

⇩

High Voltage Shock – Delivered on demand



L
+
ICD
SVC coil
Shock
vector
–
RV coil

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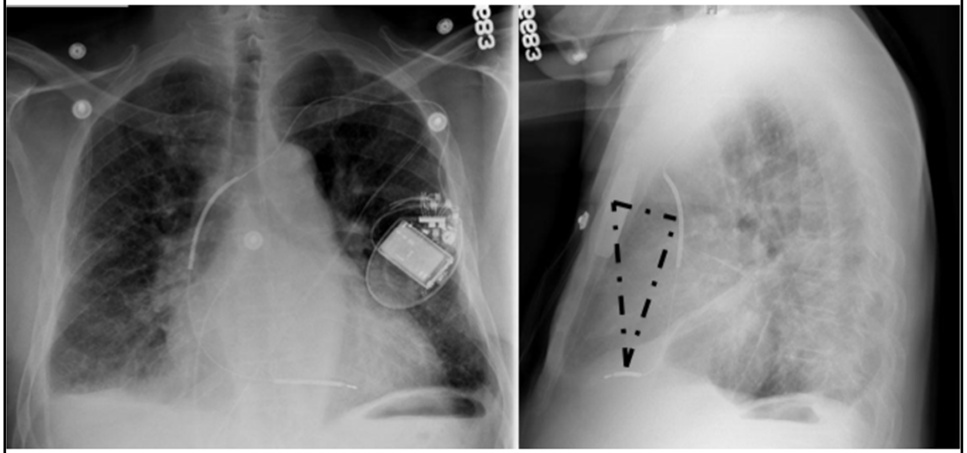

How does it know what to shock?

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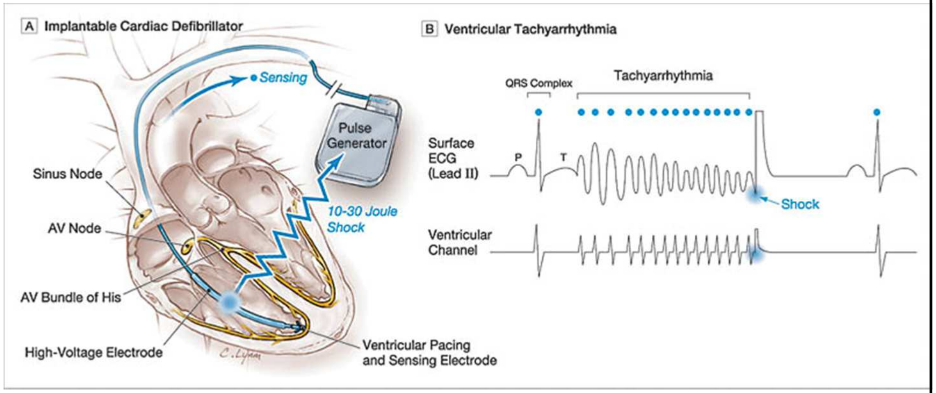
A Implantable Cardiac Defibrillator
Sensing
Pulse Generator
Sinus Node
AV Node
10-30 Joule Shock
AV Bundle of His
High-Voltage Electrode
Ventricular Pacing and Sensing Electrode
B Ventricular Tachyarrhythmia
QRS Complex
Tachyarrhythmia
Surface ECG (Lead II)
P
T
Shock
Ventricular Channel

Sensing

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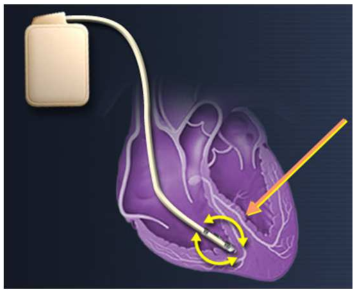

- The 'eye' of the device
  - –Constantly watches for electrical activity
  - –Sees or Senses all electrical signals that pass
  - –Signal produced by a passing electrical wave is called an Intracardiac Electrogram (EGM)

Subcutaneous ICD

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- Requires no venous access
- Is designed to hopefully reduce complications
- Requires no fluoroscopy
- An option for a majority of primary and secondary ICD candidates
- Alternative for TV-ICD replacements due to lead malfunction/infection
- Appropriate for a broad range of body types

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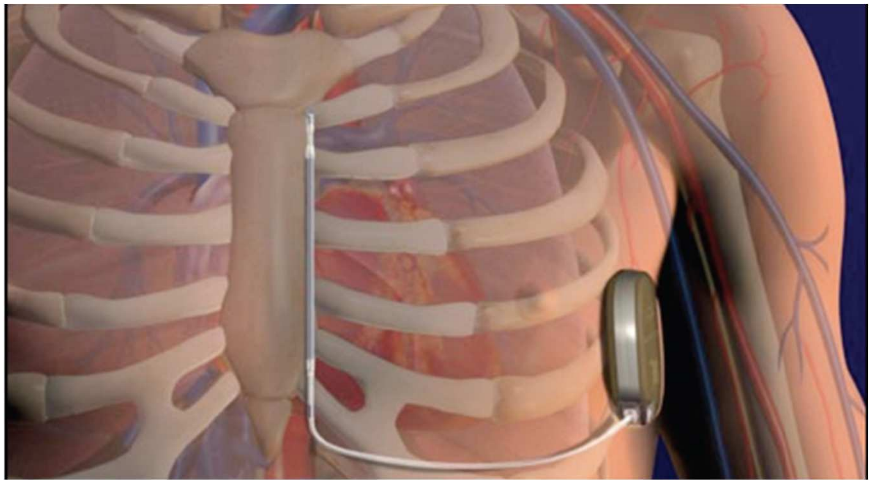

Major Implantable Cardioverter-Defibrillator Trials for Prevention of Sudden Cardiac Death

Trial	Year	Patients (n)	Inclusion Criterion: LVEF	Additional Study Features	Hazard Ratio*	95% CI	p
MADIT I	1996	196	≤ 35%	NSVT and EP+	0.46	(0.26-0.82)	p=0.009
MADIT II	2002	1232	≤ 30%	Prior MI	0.69	(0.51-0.93)	p=0.016
CABG-Patch	1997	900	< 36%	+SAECG and CABG	1.07	(0.81-1.42)	p=0.64
DEFINITE	2004	485	< 36%	NICM, PVCs or NSVT	0.65	(0.40-1.06)	p=0.08
DINAMIT	2004	674	≤ 35%	6-40 days post-MI and Impaired HRV	1.08	(0.76-1.55)	p=0.66
SCD-HeFT	2006	1676	≤ 35%	Prior MI or NICM	0.77	(0.62-0.96)	p=0.007
AVID	1997	1016	≤ 40%	Prior cardiac Arrest, or Unstable VT	0.62	(0.43-0.82)	p<0.02
CASH†	2000	191	Mean ≤ 45% ±18 at baseline	Prior cardiac arrest	0.766	‡	1-sided p=0.081
CIDS	2000	659	≤ 35%	Prior cardiac Arrest, Unstable VT, or Syncope	0.82	(0.60-1.1)	NS

* Hazard ratios for death from any cause in the ICD group compared with the non-ICD group. †Includes only ICD and amiodarone patients from CASH.
‡CI Upper Bound 1.112. CI indicates Confidence Interval, EP+ = positive electrophysiologic study, HRV = heart rate variability, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NICM = nonischemic cardiomyopathy, NS = Not statistically significant, NSVT = nonsustained ventricular tachycardia, PVCs = premature ventricular contractions, SAECG = signal-averaged electrocardiogram, VT = ventricular tachycardia.

Epstein A, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. J Am Coll Cardiol 2008; 51:e1–62. Table 5.

Centers for Medicare & Medicaid Services (CMS)

- ICD coverage decision based on MADIT II, SCD-HeFT finalized early 2005

Centers for Medicare & Medicaid Services (CMS)

- Documented VT/VF arrest not due to transient cause
- Documented familial or inherited condition associated with a high risk of ventricular arrhythmias (e.g., Long QT, HOCM)
- Prior MI, LVEF ≤ 35%, NSVT, inducible VT at EP study
- Ischemic CM, LVEF ≤ 30%
- Ischemic CM, LVEF ≤ 35% and class II or III CHF
- Non-ischemic CM, EF ≤ 35% for > 3 months, class II or III CHF

Centers for Medicare & Medicaid Services (CMS)

- Patients must NOT have
  - PTCA or CABG within past 3 months
  - Acute MI within past 40 days
  - Clinical symptoms making them candidates for revascularization
  - Other disease (non-cardiac) with a life expectancy < 1 year

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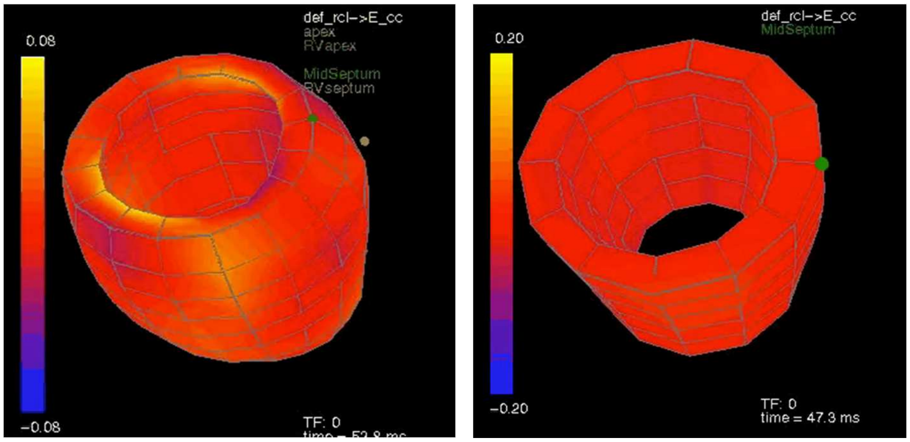
aka BiV

CARDIAC RESYNCHRONIZATION THERAPY (CRT)


def_rcl->E_cc
apex
RVapex
MidSeptum
RVseptum
0.08
−0.08
TF: 0
def_rcl->E_cc
MidSeptum
0.20
−0.20
TF: 0
time = 47.3 ms

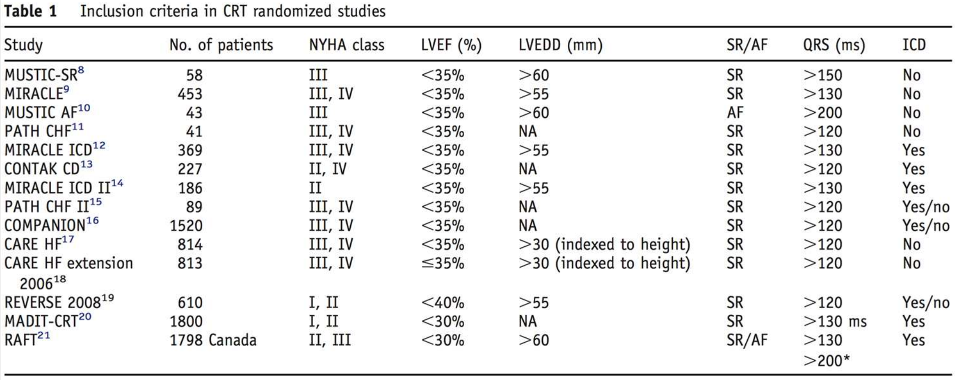


Table 1 Inclusion criteria in CRT randomized studies

Study	No. of patients	NYHA class	LVEF (%)	LVEDD (mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR[8]	58	III	<35%	>60	SR	>150	No
MIRACLE[9]	453	III, IV	<35%	>55	SR	>130	No
MUSTIC AF[10]	43	III	<35%	>60	AF	>200	No
PATH CHF[11]	41	III, IV	<35%	NA	SR	>120	No
MIRACLE ICD[12]	369	III, IV	<35%	>55	SR	>130	Yes
CONTAK CD[13]	227	II, IV	<35%	NA	SR	>120	Yes
MIRACLE ICD II[14]	186	II	<35%	>55	SR	>130	Yes
PATH CHF II[15]	89	III, IV	<35%	NA	SR	>120	Yes/no
COMPANION[16]	1520	III, IV	<35%	NA	SR	>120	Yes/no
CARE HF[17]	814	III, IV	<35%	>30 (indexed to height)	SR	>120	No
CARE HF extension 2006[18]	813	III, IV	≤35%	>30 (indexed to height)	SR	>120	No
REVERSE 2008[19]	610	I, II	<40%	>55	SR	>120	Yes/no
MADIT-CRT[20]	1800	I, II	<30%	NA	SR	>130 ms	Yes
RAFT[21]	1798 Canada	II, III	<30%	>60	SR/AF	>130 >200*	Yes

Heart Rhythm 2012

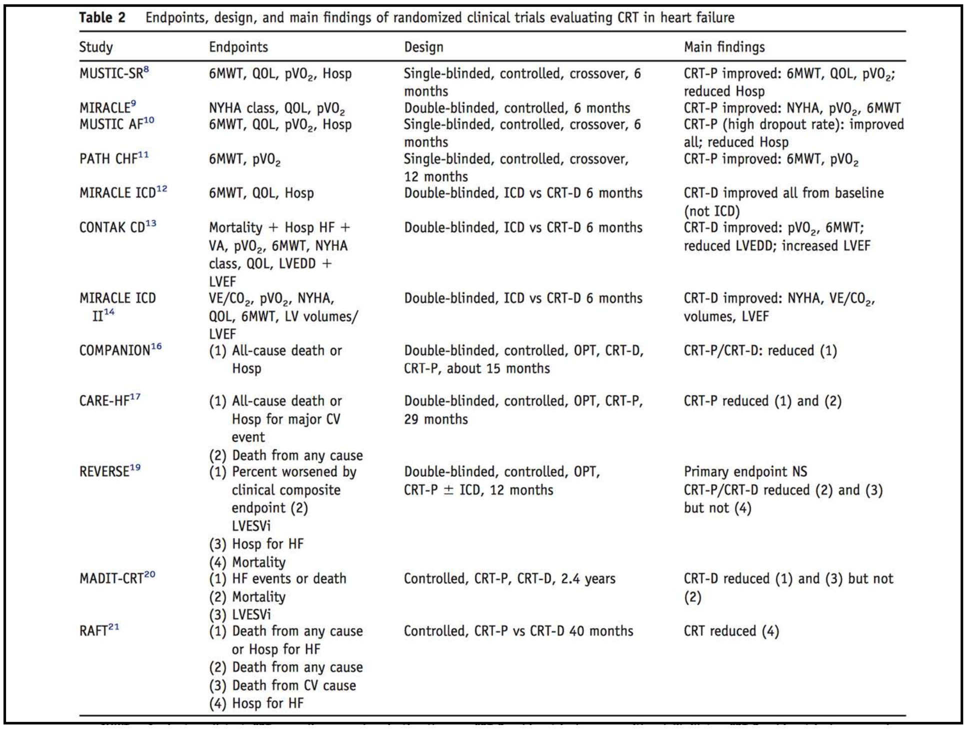


Table 2 Endpoints, design, and main findings of randomized clinical trials evaluating CRT in heart failure

Study	Endpoints	Design	Main findings
MUSTIC-SR[8]	6MWT, QOL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved: 6MWT, QOL, pVO_2; reduced Hosp
MIRACLE[9]	NYHA class, QOL, pVO_2	Double-blinded, controlled, 6 months	CRT-P improved: NYHA, pVO_2, 6MWT
MUSTIC AF[10]	6MWT, QOL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P (high dropout rate): improved all; reduced Hosp
PATH CHF[11]	6MWT, pVO_2	Single-blinded, controlled, crossover, 12 months	CRT-P improved: 6MWT, pVO_2
MIRACLE ICD[12]	6MWT, QOL, Hosp	Double-blinded, ICD vs CRT-D 6 months	CRT-D improved all from baseline (not ICD)
CONTAK CD[13]	Mortality + Hosp HF + VA, pVO_2, 6MWT, NYHA class, QOL, LVEDD + LVEF	Double-blinded, ICD vs CRT-D 6 months	CRT-D improved: pVO_2, 6MWT; reduced LVEDD; increased LVEF
MIRACLE ICD II[14]	VE/CO_2, pVO_2, NYHA, QOL, 6MWT, LV volumes/ LVEF	Double-blinded, ICD vs CRT-D 6 months	CRT-D improved: NYHA, VE/CO_2, volumes, LVEF
COMPANION[16]	(1) All-cause death or Hosp	Double-blinded, controlled, OPT, CRT-D, CRT-P, about 15 months	CRT-P/CRT-D: reduced (1)
CARE-HF[17]	(1) All-cause death or Hosp for major CV event (2) Death from any cause	Double-blinded, controlled, OPT, CRT-P, 29 months	CRT-P reduced (1) and (2)
REVERSE[19]	(1) Percent worsened by clinical composite endpoint (2) LVESVi (3) Hosp for HF (4) Mortality	Double-blinded, controlled, OPT, CRT-P ± ICD, 12 months	Primary endpoint NS CRT-P/CRT-D reduced (2) and (3) but not (4)
MADIT-CRT[20]	(1) HF events or death (2) Mortality (3) LVESVi	Controlled, CRT-P, CRT-D, 2.4 years	CRT-D reduced (1) and (3) but not (2)
RAFT[21]	(1) Death from any cause or Hosp for HF (2) Death from any cause (3) Death from CV cause (4) Hosp for HF	Controlled, CRT-P vs CRT-D 40 months	CRT reduced (4)

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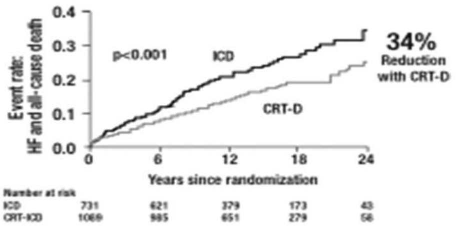

Figure 3 MADIT-CRT—significant reduction in relative risk of sustaining a primary endpoint with CRT-D. CRT = cardiac resynchronization therapy; HF = heart failure. Adapted from Moss et al.[20]

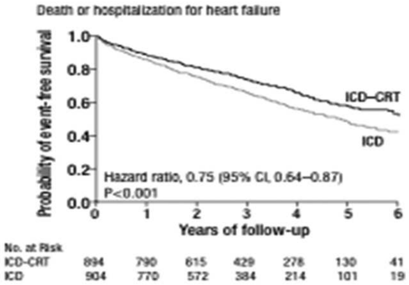

Figure 5 RAFT—primary endpoint. CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator. Adapted from Tang et al.[21]

Achieving Cardiac Resynchronization

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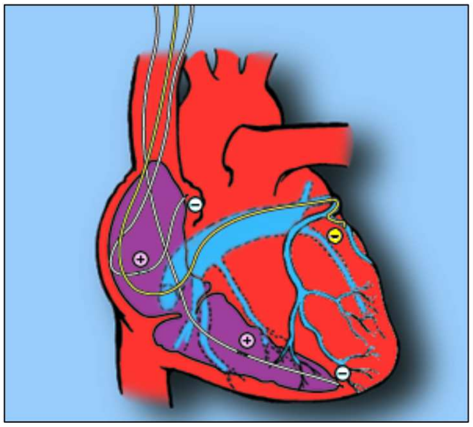
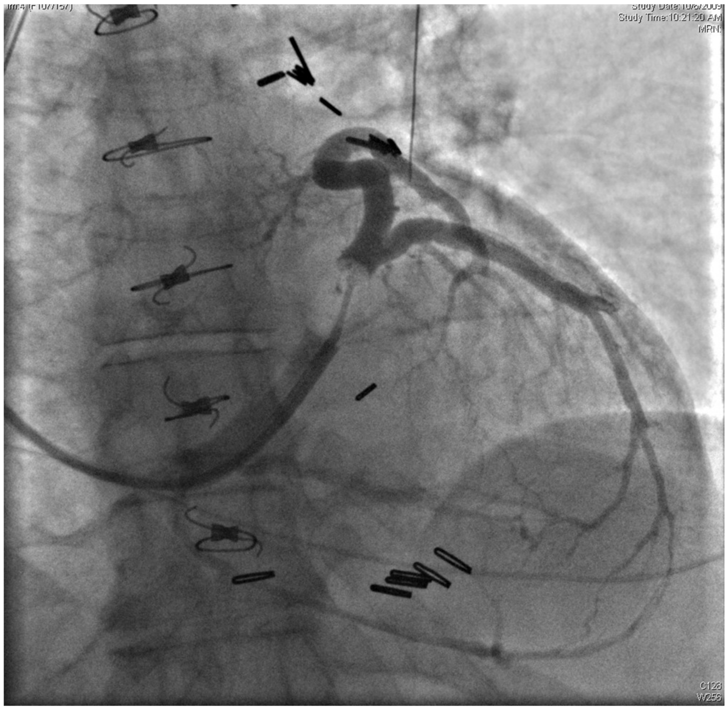
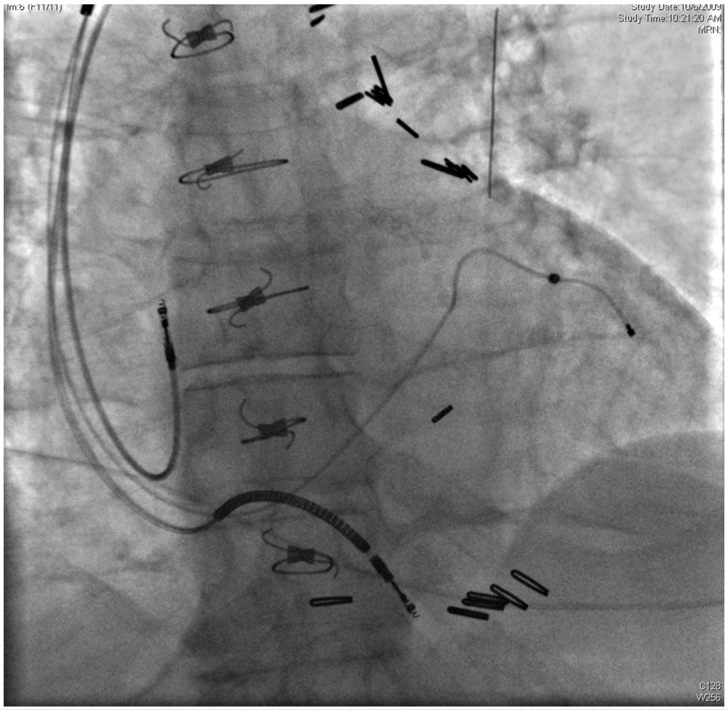
Goal: Pace Right and Left Ventricles

- Epicardial Approach
  - Requires thoracotomy
- Transvenous Approach
  - Requires access to the coronary sinus
  - Requires leads developed for LV application



1. **Bakker et al.** ***J of Cardiac Failure*** **1998; 4[3]:1-35**
2. **Saxon et al.** ***PACE*** **1998; 21 Part II: 914**
3. **Daubert et al.** ***PACE*** **1997; 20[II]**
4. **Gras et al.** ***PACE*** **1998; 21[II]:824**




Im:5 (F11/11)
Study Date:10/6/2009
Study Time:10:21:20 AM
MRN:
C128
W256

Baseline ECG

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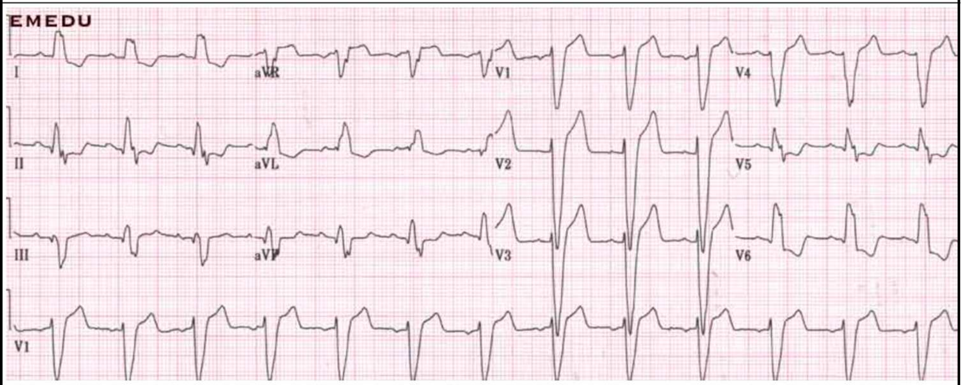
EMEDU
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

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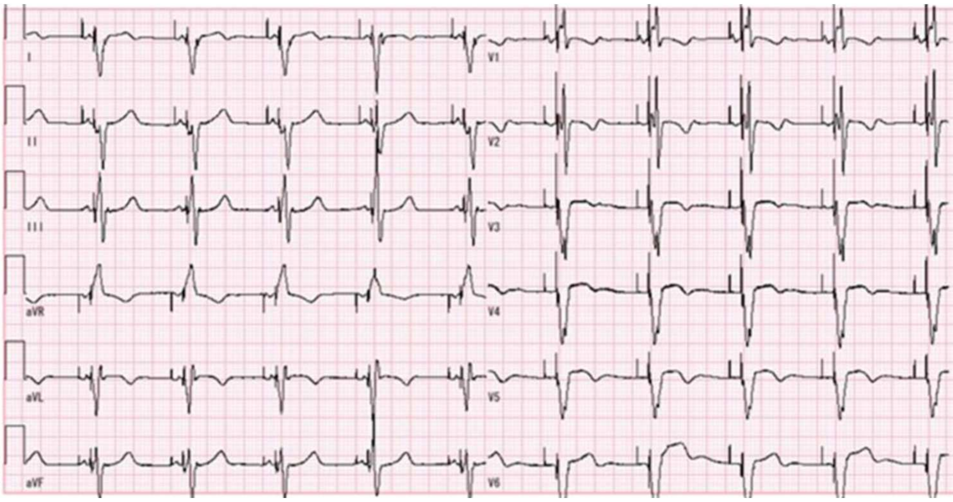
Post-CRT EKG



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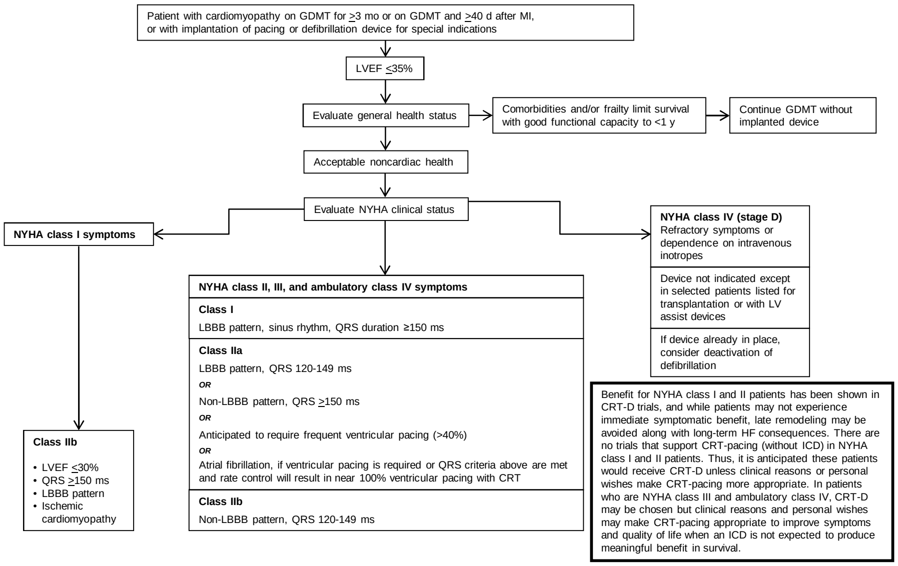
Indications for CRT Therapy—Algorithm



Patient with cardiomyopathy on GDMT for ≥3 mo or on GDMT and ≥40 d after MI, or with implantation of pacing or defibrillation device for special indications

LVEF ≤35%

Evaluate general health status

Comorbidities and/or frailty limit survival with good functional capacity to <1 y

Continue GDMT without implanted device

Acceptable noncardiac health

Evaluate NYHA clinical status

NYHA class I symptoms

Class IIb

- LVEF ≤30%
- QRS ≥150 ms
- LBBB pattern
- Ischemic cardiomyopathy

NYHA class II, III, and ambulatory class IV symptoms

Class I

LBBB pattern, sinus rhythm, QRS duration ≥150 ms

Class IIa

LBBB pattern, QRS 120-149 ms

OR

Non-LBBB pattern, QRS ≥150 ms

OR

Anticipated to require frequent ventricular pacing (>40%)

OR

Atrial fibrillation, if ventricular pacing is required or QRS criteria above are met and rate control will result in near 100% ventricular pacing with CRT

Class IIb

Non-LBBB pattern, QRS 120-149 ms

NYHA class IV (stage D)

Refractory symptoms or dependence on intravenous inotropes

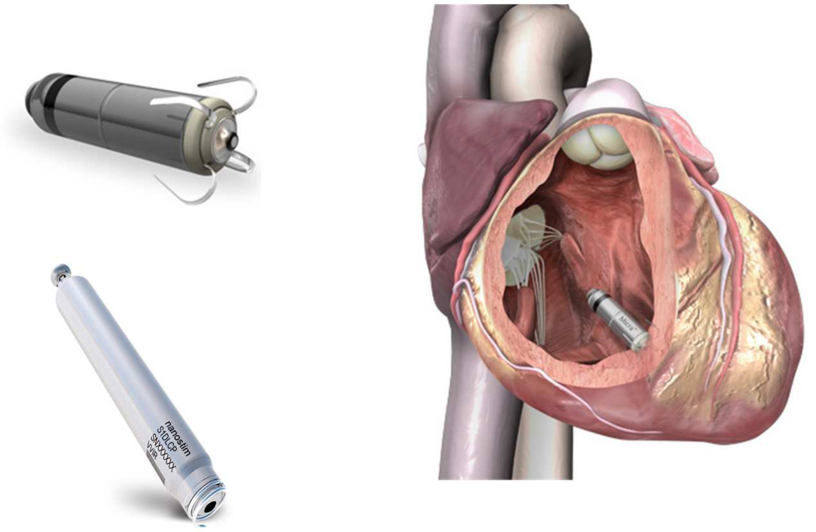
Device not indicated except in selected patients listed for transplantation or with LV assist devices

If device already in place, consider deactivation of defibrillation

Benefit for NYHA class I and II patients has been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefit in survival.

ADVANCES IN CARDIAC DEVICES

Leadless Pacemaker


nanostim
S1DLCP
SNXXXXXX
VVIR

- Nanostim (SJM) first leadless ppm to enter market (October 2013)
- FDA approval of Micra Transcatheter Pacing System (MDT) – April 2016
- Voluntary pause of Nanostim implants due to battery concerns
- U.S. Centers for Medicare & Medicaid Services (CMS) approved reimbursement coverage for Micra – March 2017*

*when used in accordance with FDA-approved labeling in FDA-approved studies

---

- FDA approved indications:
  - symptomatic paroxysmal/permanent high-grade AVB in the presence of AF
  - symptomatic paroxysmal/permanent high-grade AVB in the absence of AF, when atrial lead placement considered difficult, high risk or not necessary for effective therapy
  - symptomatic SND, when atrial lead placement is considered difficult, high risk, or not deemed necessary
- Advantages: Avoid potential complications of traditional ppm including pocket infections, erosion of the pacemaker through the skin, lead dislodgement and lead fracture or perforation

- Contraindicated in patients with:
  - implanted IVC filter
  - mechanical tricuspid valve
  - another CIED that might interfere with sensing
  - femoral venous anatomy unable to accommodate 23Fr introducer sheath
  - obesity (>4.9 in between chest & header)
  - intolerance to heparin

DEVICE IDENTIFICATION

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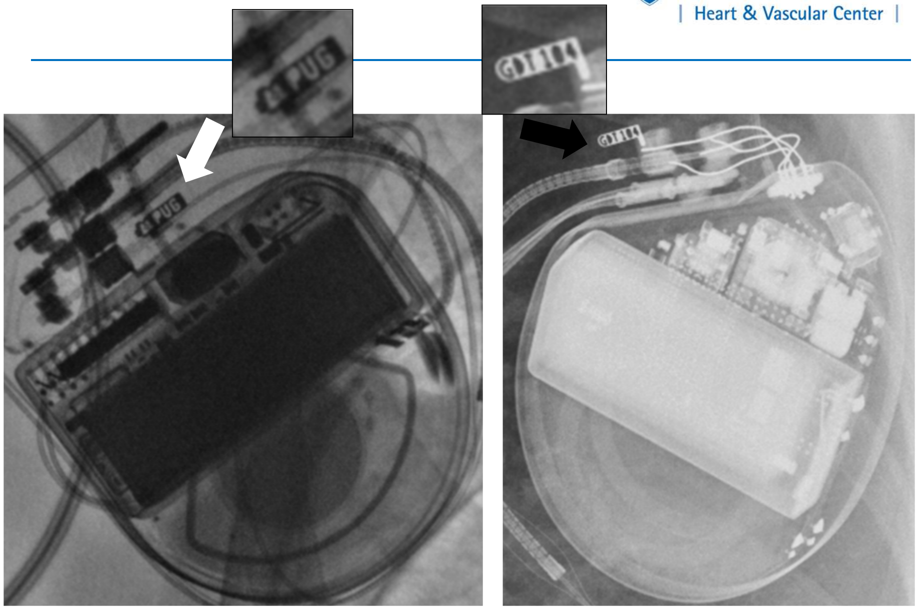

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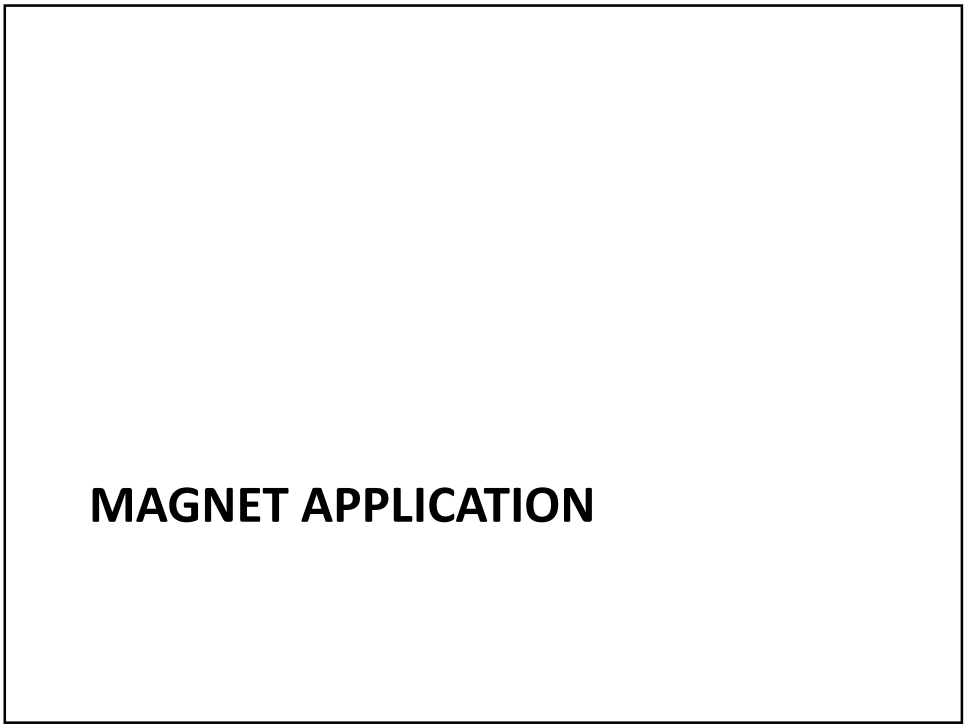
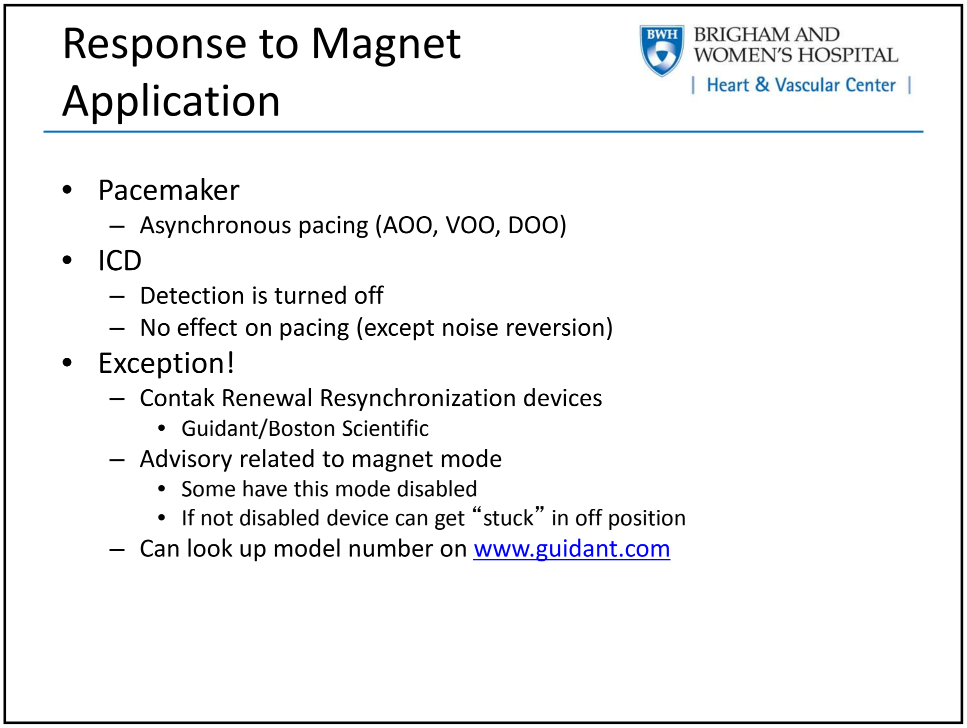
Table 1. Device Manufacturers' Contact Information

Medtronic	1.800.MEDTRONIC
Boston Scientific	1.800.CARDIAC
St. Jude Medical	1.800.PACEICD
Biotronik	1.800.547.0394
Sorin Group	1.800.352.6466



MAGNET APPLICATION



Response to Magnet Application

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- Pacemaker
  - Asynchronous pacing (AOO, VOO, DOO)
- ICD
  - Detection is turned off
  - No effect on pacing (except noise reversion)
- Exception!
  - Contak Renewal Resynchronization devices
    - Guidant/Boston Scientific
  - Advisory related to magnet mode
    - Some have this mode disabled
    - If not disabled device can get "stuck" in off position
  - Can look up model number on www.guidant.com

DEVICE TROUBLESHOOTING

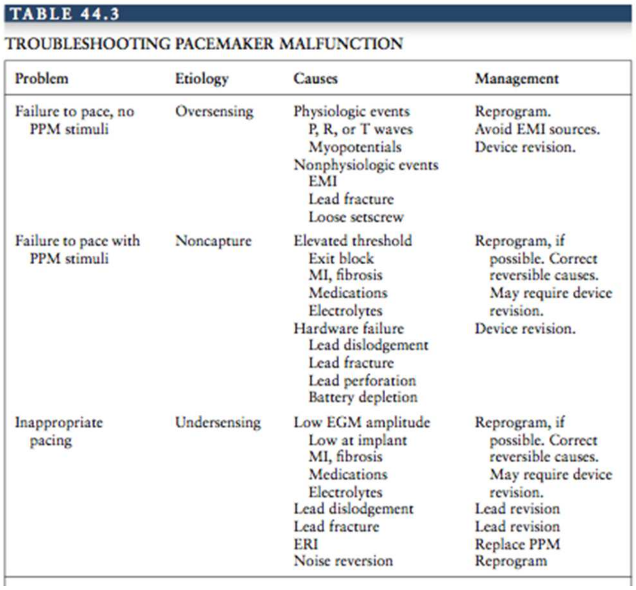

TABLE 44.3

TROUBLESHOOTING PACEMAKER MALFUNCTION

Problem	Etiology	Causes	Management
Failure to pace, no PPM stimuli	Oversensing	Physiologic events P, R, or T waves Myopotentials Nonphysiologic events EMI Lead fracture Loose setscrew	Reprogram. Avoid EMI sources. Device revision.
Failure to pace with PPM stimuli	Noncapture	Elevated threshold Exit block MI, fibrosis Medications Electrolytes Hardware failure Lead dislodgement Lead fracture Lead perforation Battery depletion	Reprogram, if possible. Correct reversible causes. May require device revision. Device revision.
Inappropriate pacing	Undersensing	Low EGM amplitude Low at implant MI, fibrosis Medications Electrolytes Lead dislodgement Lead fracture ERI Noise reversion	Reprogram, if possible. Correct reversible causes. May require device revision. Lead revision Lead revision Replace PPM Reprogram

DEVICE TROUBLESHOOTING: OVERSENSING

Sensing

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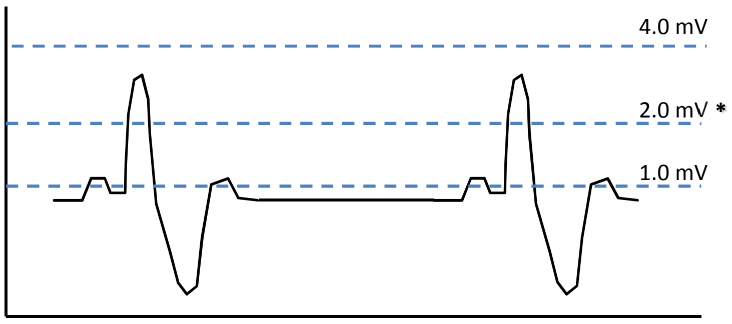
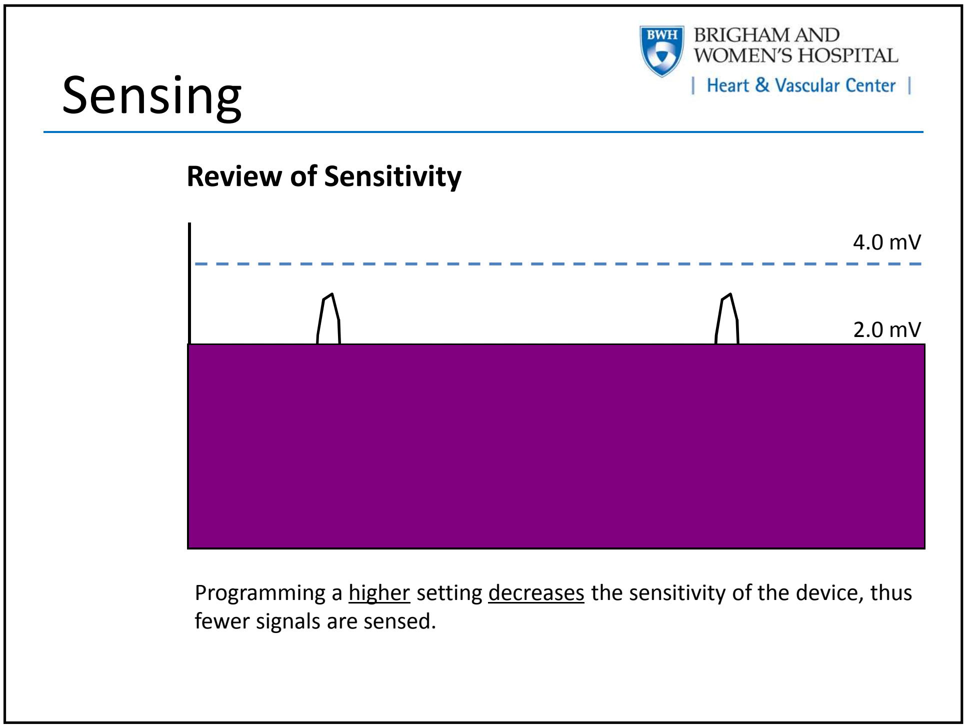
Review of Sensitivity



*programmed sensitivity



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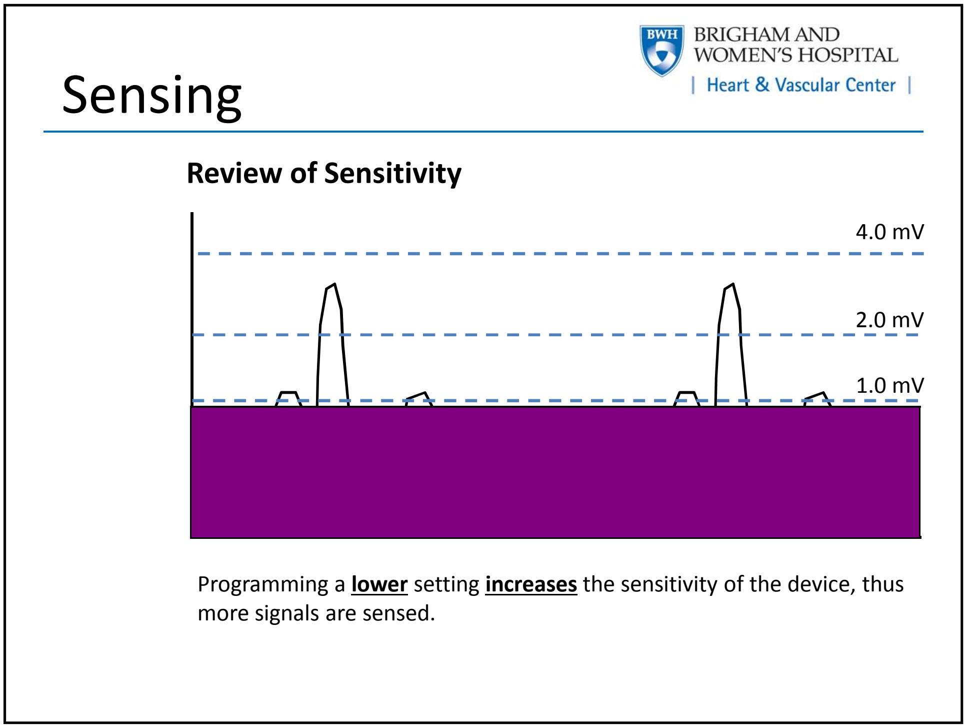
Sensing

Review of Sensitivity

Programming a higher setting decreases the sensitivity of the device, thus fewer signals are sensed.



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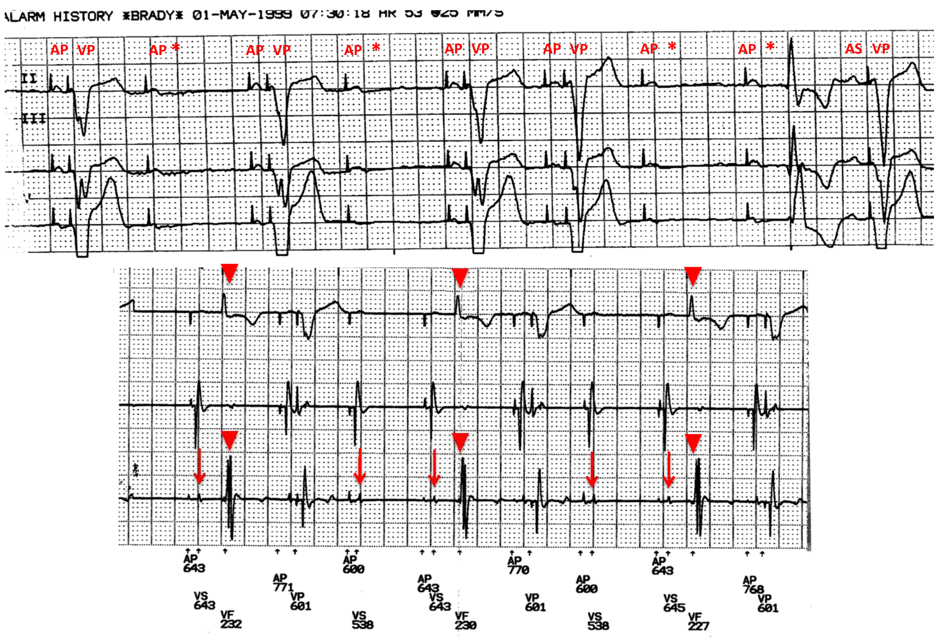
Sensing

Review of Sensitivity

Programming a **lower** setting **increases** the sensitivity of the device, thus more signals are sensed.


ALARM HISTORY *BRADY* 01-MAY-1999 07:30:18 HR 53 @25 MM/S
AP VP
AP *
AP VP
AP *
AP VP
AP VP
AP *
AP *
AS VP
II
III
AP 643
VS 643
VF 232
AP 771
VP 601
AP 600
VS 538
AP 643
VS 643
VF 230
AP 770
VP 601
AP 600
VS 538
AP 643
VS 645
VF 227
AP 768
VP 601

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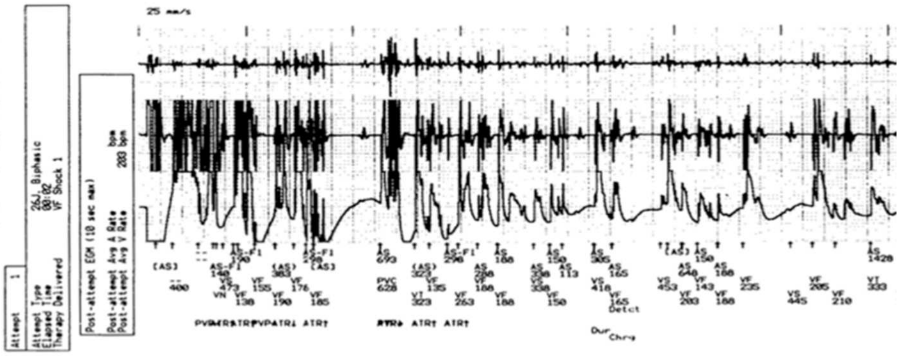
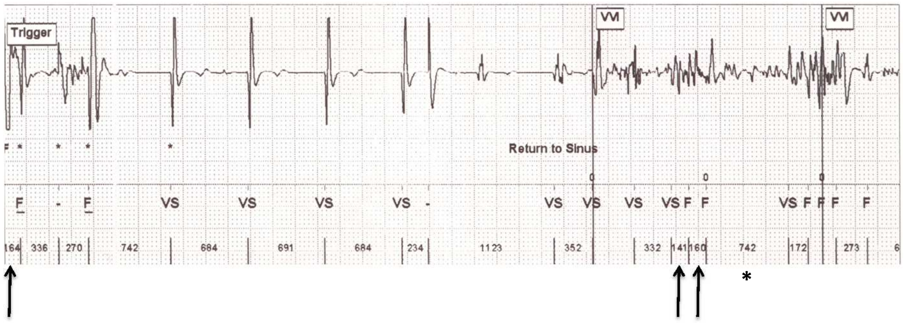
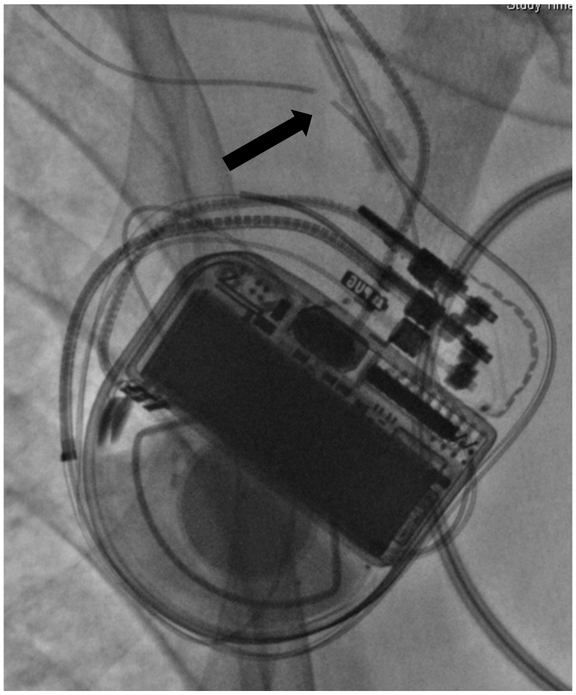

Attempt 1
Attempt Type 26J, Biphasic
Elapsed Time 00:02
Therapy Delivered VF Shock 1
Post-attempt EGM (10 sec max)
Post-attempt Avg A Rate bpm
Post-attempt Avg V Rate 203 bpm
25 mm/s
(AS)
PVC
VT
VF
VS
AS
Dur Chrg
Detct


Trigger
VVI
VVI
F * * * *
Return to Sinus
0 0 0
F - F VS VS VS VS - VS VS VS VS F F VS F F F F
164 336 270 742 684 691 684 234 1123 352 332 141 160 742 172 273 6
*


Study Time

DEVICE TROUBLESHOOTING: NONCAPTURE

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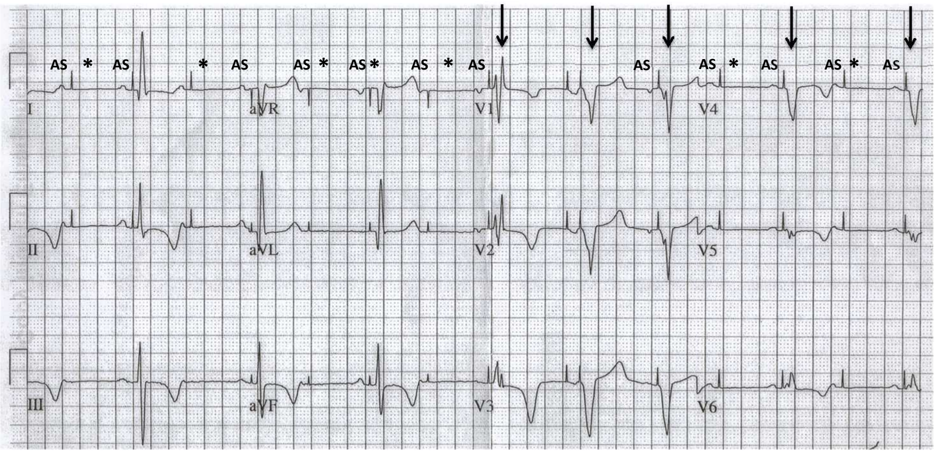
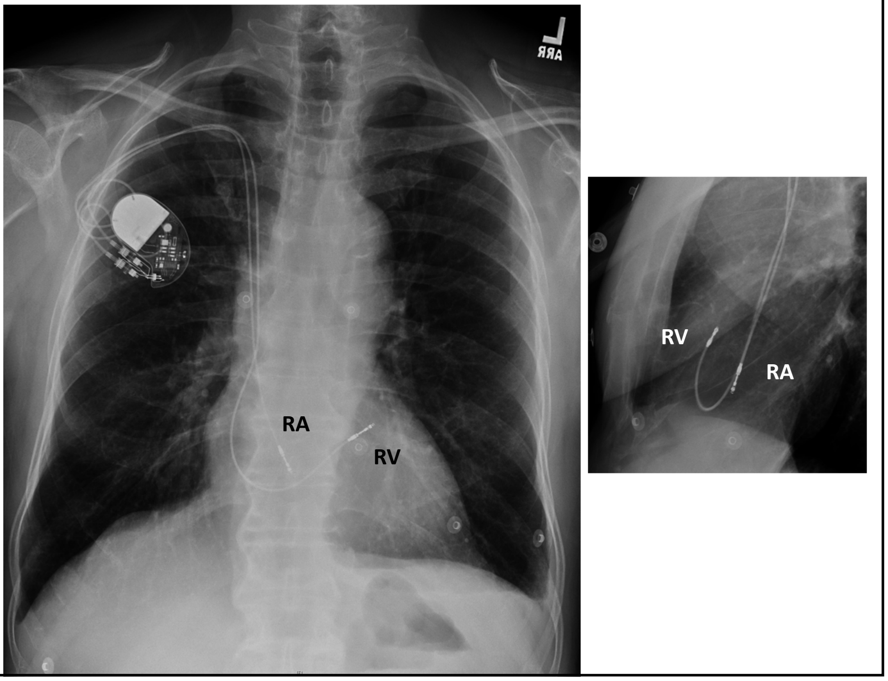
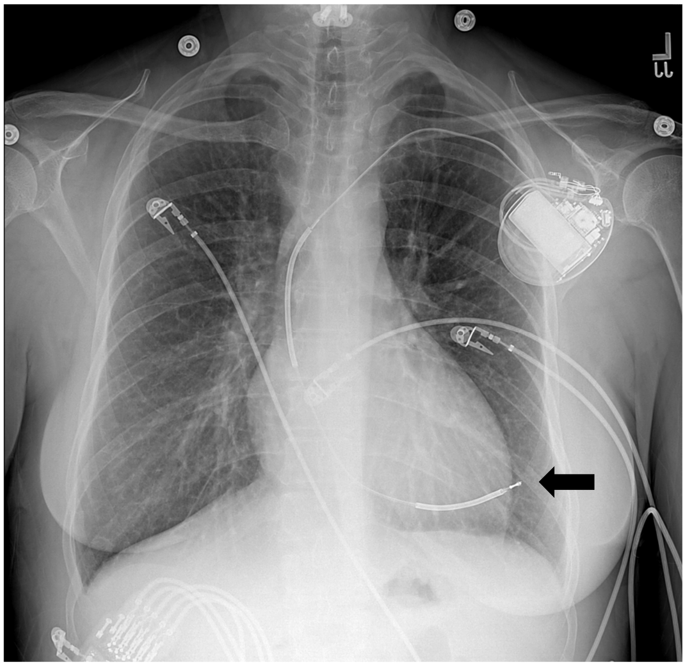

AS * AS * AS AS * AS * AS * AS AS AS * AS AS * AS
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6


RA
RV
RV
RA



DEVICE TROUBLESHOOTING: UNDERSENSING

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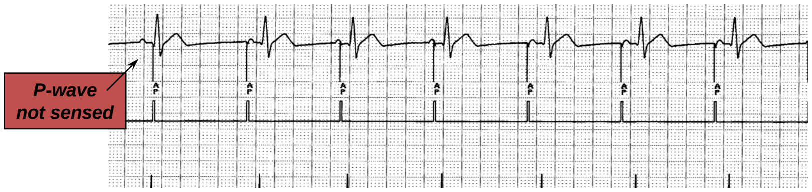
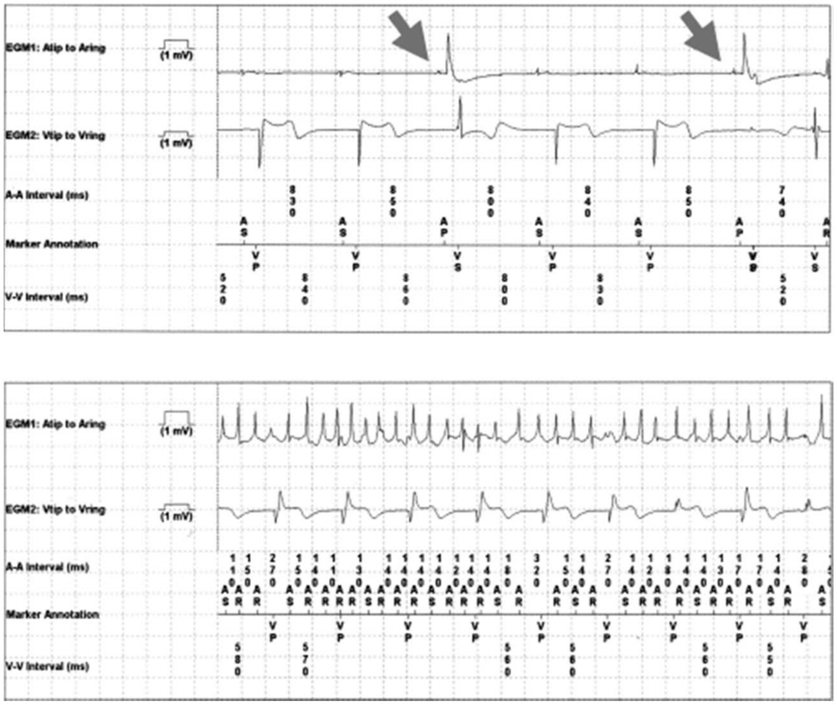
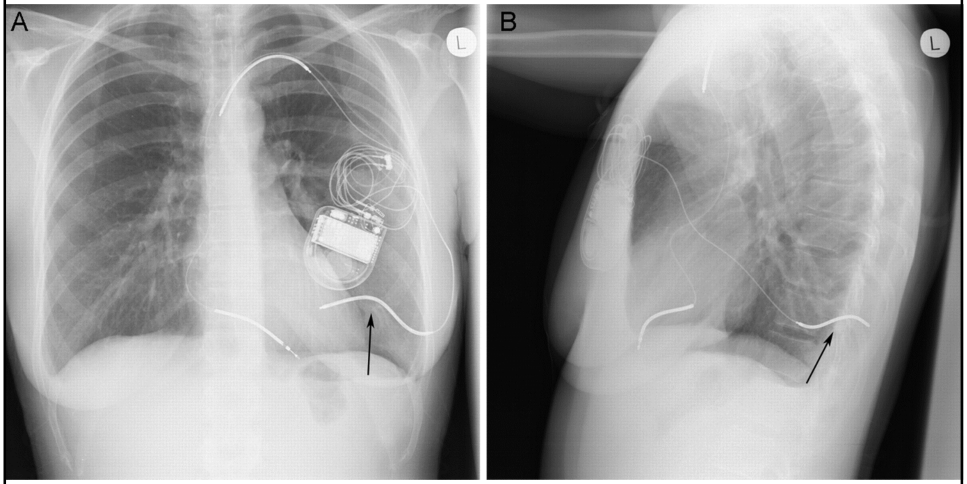
- An intrinsic depolarization that is present, yet not seen or sensed by the pacemaker

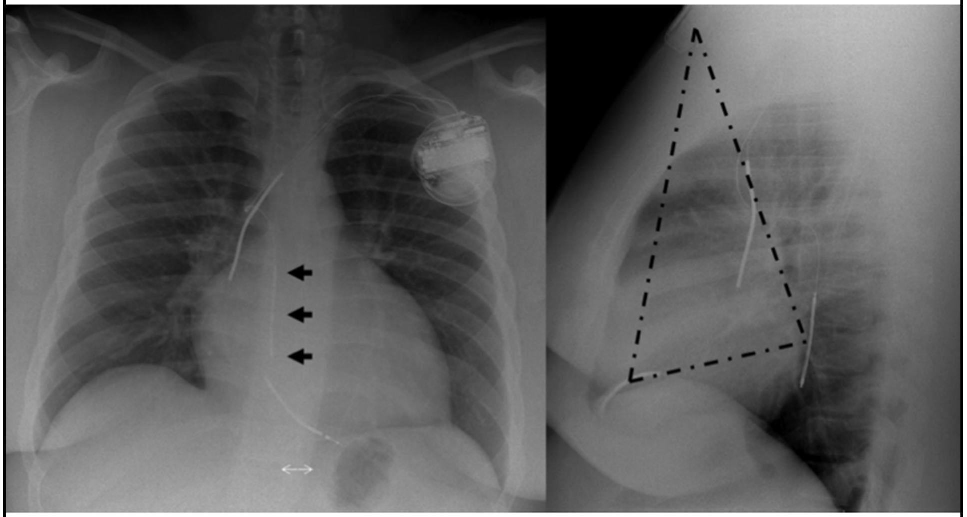


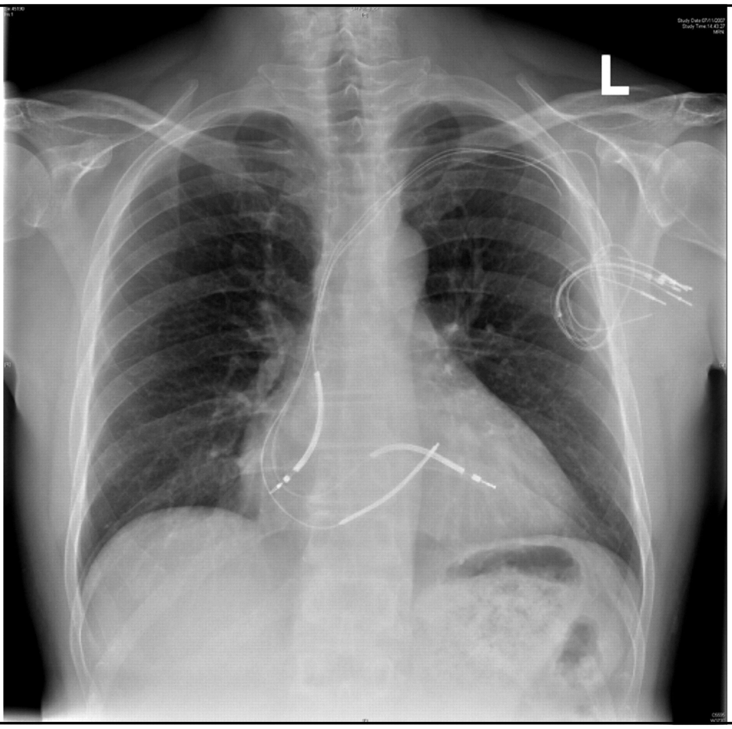
Atrial Undersensing


EGM1: Atip to Aring
(1 mV)
EGM2: Vtip to Vring
(1 mV)
A-A Interval (ms)
Marker Annotation
V-V Interval (ms)
EGM1: Atip to Aring
(1 mV)
EGM2: Vtip to Vring
(1 mV)
A-A Interval (ms)
Marker Annotation
V-V Interval (ms)

INEFFECTIVE DEFIBRILLATION


A
L
B
L





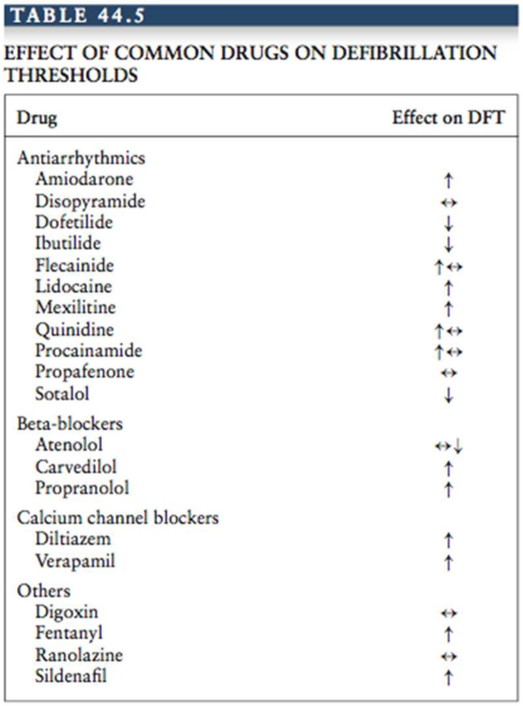


TABLE 44.5

EFFECT OF COMMON DRUGS ON DEFIBRILLATION THRESHOLDS

Drug	Effect on DFT
Antiarrhythmics	
Amiodarone	↑
Disopyramide	↔
Dofetilide	↓
Ibutilide	↓
Flecainide	↑↔
Lidocaine	↑
Mexilitine	↑
Quinidine	↑↔
Procainamide	↑↔
Propafenone	↔
Sotalol	↓
Beta-blockers	
Atenolol	↔↓
Carvedilol	↑
Propranolol	↑
Calcium channel blockers	
Diltiazem	↑
Verapamil	↑
Others	
Digoxin	↔
Fentanyl	↑
Ranolazine	↔
Sildenafil	↑

INAPPROPRIATE SHOCKS

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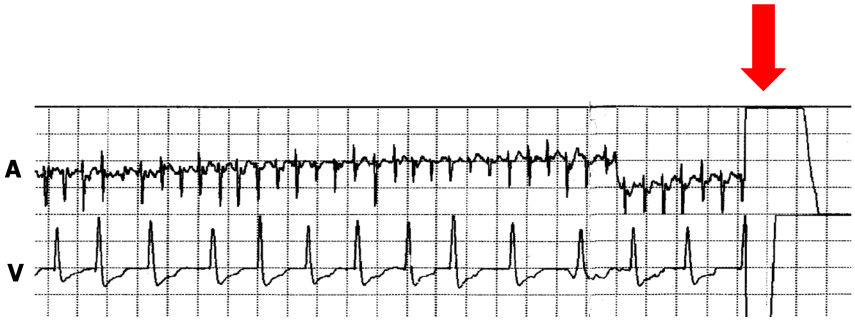

BRIGHAM AND WOMEN'S HOSPITAL

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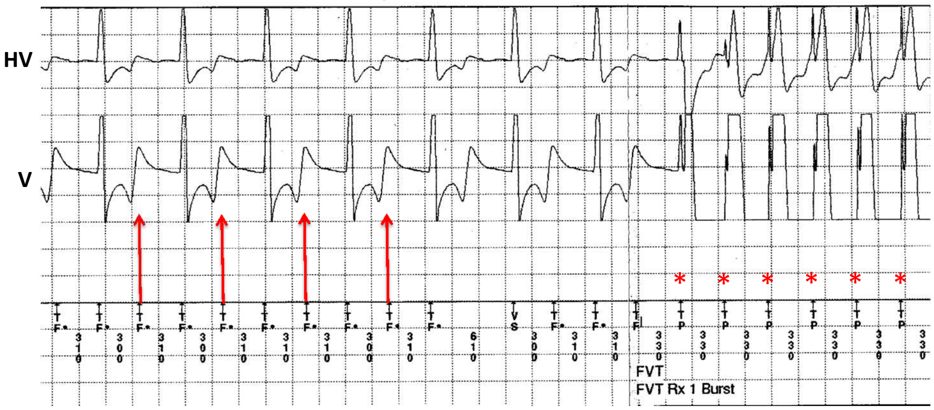
HV
V
FVT
FVT Rx 1 Burst

LOSS OF RESYNCHRONIZATION

Baseline ECG

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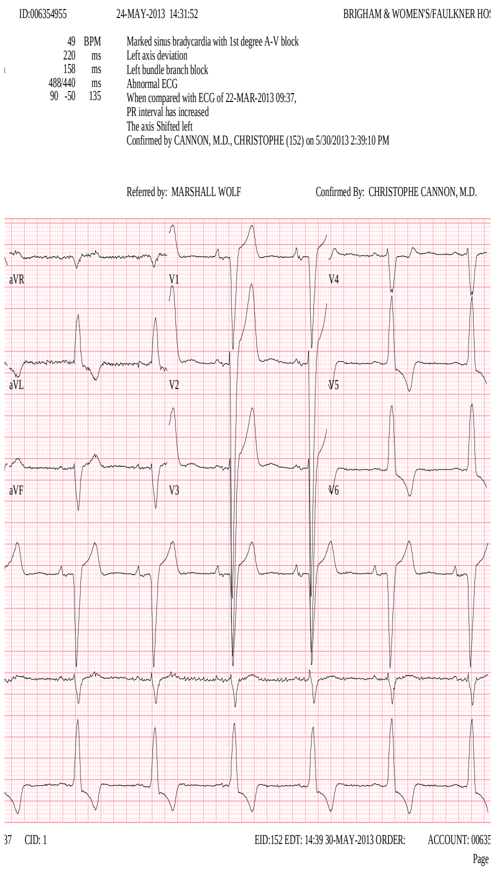
ID:006354955 24-MAY-2013 14:31:52 BRIGHAM & WOMEN'S/FAULKNER HO

49 BPM Marked sinus bradycardia with 1st degree A-V block
220 ms Left axis deviation
158 ms Left bundle branch block
488/440 ms Abnormal ECG
90 -50 135 When compared with ECG of 22-MAR-2013 09:37,
PR interval has increased
The axis Shifted left
Confirmed by CANNON, M.D., CHRISTOPHE (152) on 5/30/2013 2:39:10 PM

Referred by: MARSHALL WOLF Confirmed By: CHRISTOPHE CANNON, M.D.

37 CID: 1 EID:152 EDT: 14:39 30-MAY-2013 ORDER: ACCOUNT: 0063
Page

With CRT

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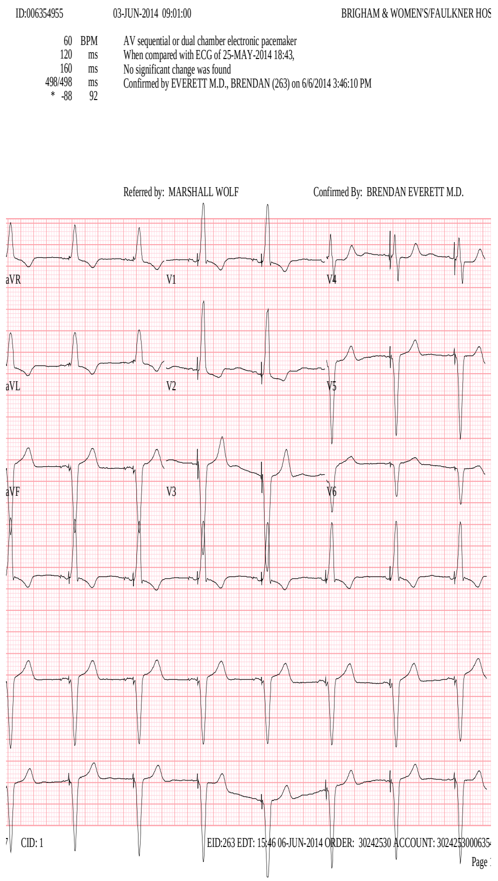
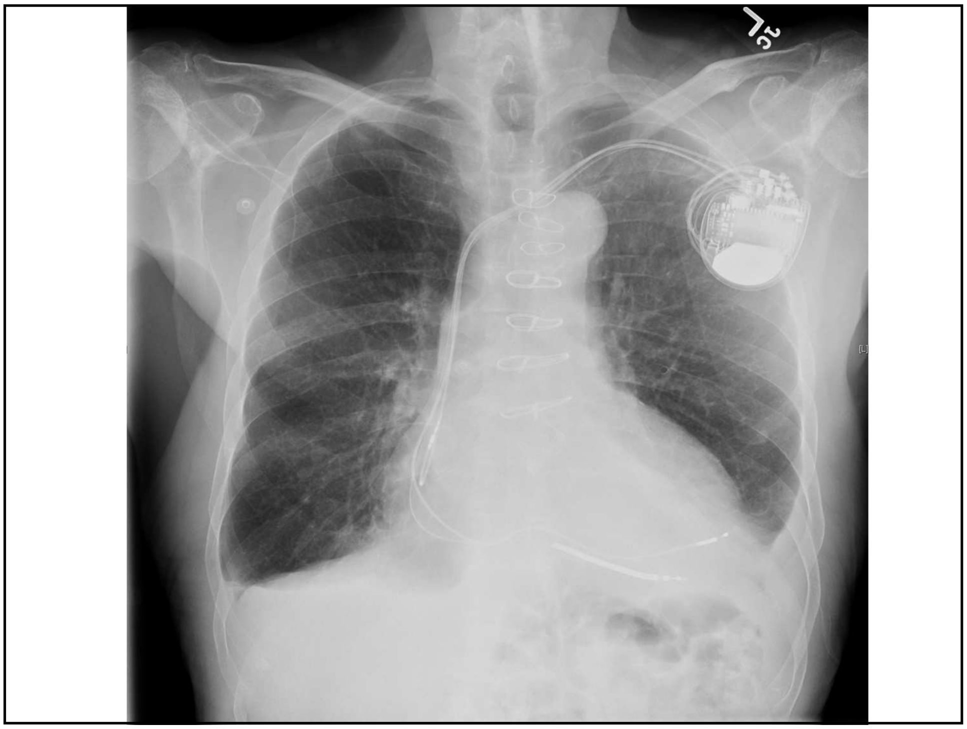
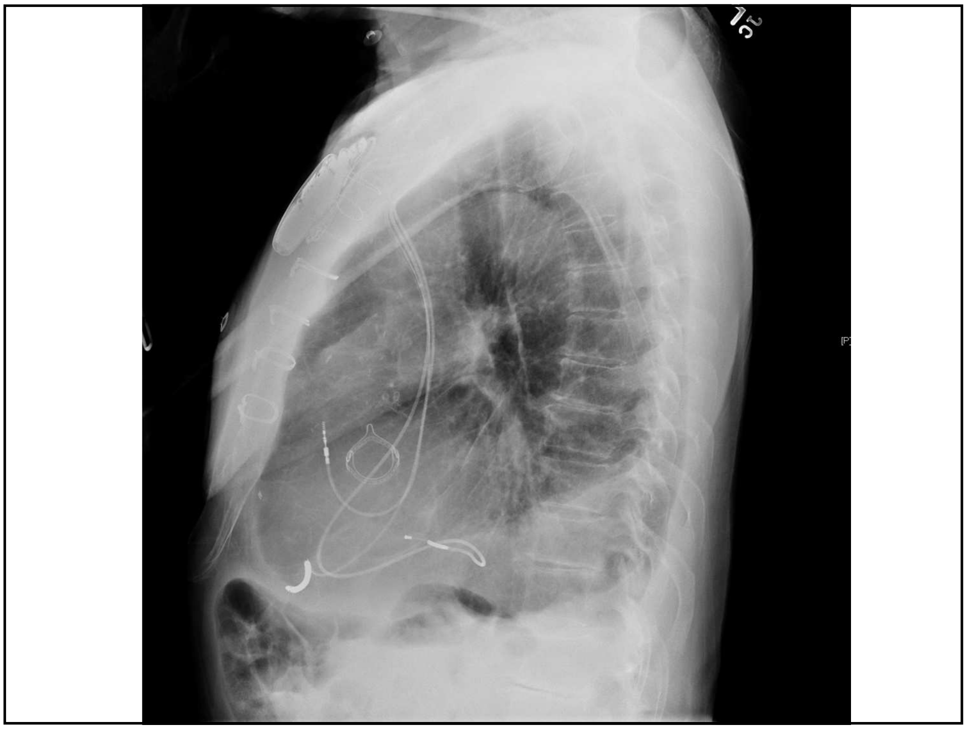

ID:006354955 03-JUN-2014 09:01:00 BRIGHAM & WOMEN'S/FAULKNER HOS

60 BPM AV sequential or dual chamber electronic pacemaker
120 ms When compared with ECG of 25-MAY-2014 18:43,
160 ms No significant change was found
498/498 ms Confirmed by EVERETT M.D., BRENDAN (263) on 6/6/2014 3:46:10 PM
* -88 92

Referred by: MARSHALL WOLF Confirmed By: BRENDAN EVERETT M.D.

CID: 1 EID:263 EDT: 15:46 06-JUN-2014 ORDER: 30242530 ACCOUNT: 302425300063
Page





Loss of CRT

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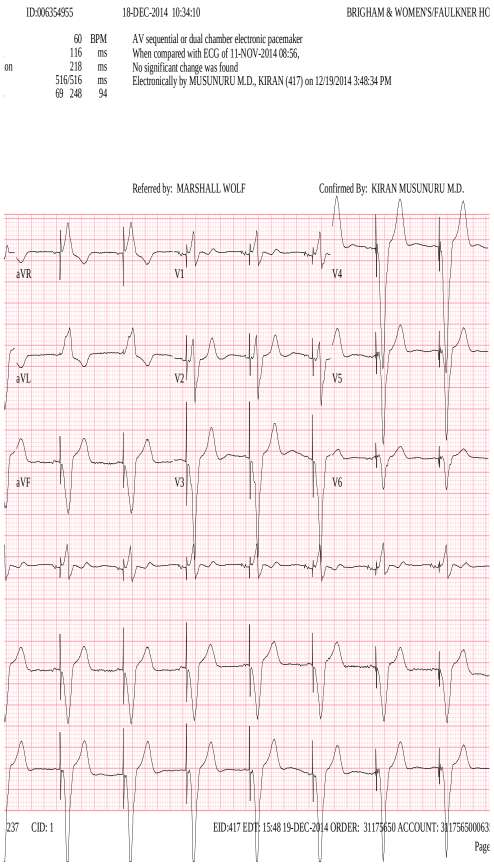


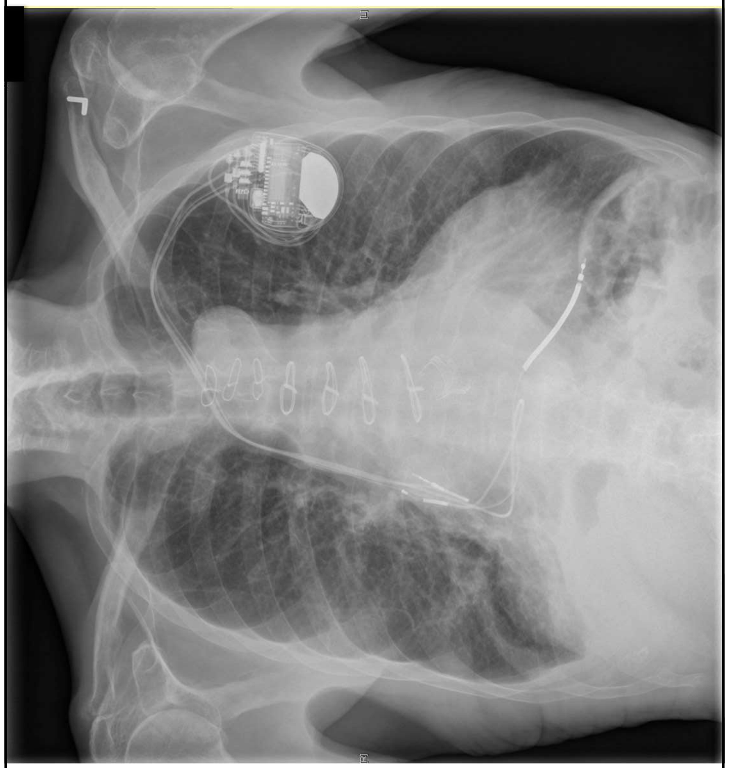
ID:006354955 18-DEC-2014 10:34:10 BRIGHAM & WOMEN'S/FAULKNER HC

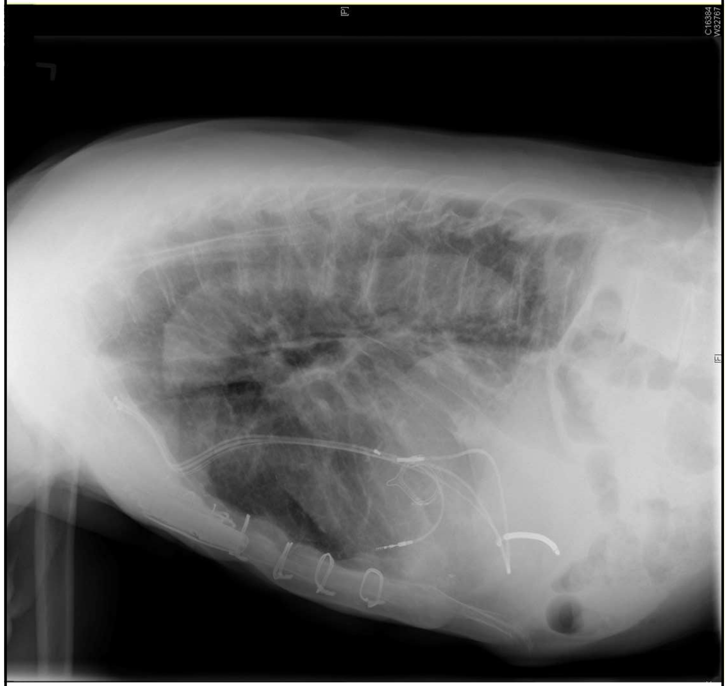
60 BPM AV sequential or dual chamber electronic pacemaker
116 ms When compared with ECG of 11-NOV-2014 08:56,
on 218 ms No significant change was found
516/516 ms Electronically by MUSUNURU M.D., KIRAN (417) on 12/19/2014 3:48:34 PM
69 248 94

Referred by: MARSHALL WOLF Confirmed By: KIRAN MUSUNURU M.D.

237 CID: 1 EID:417 EDT: 15:48 19-DEC-2014 ORDER: 31175650 ACCOUNT: 3117565000063

Page





Epicardial LV Lead

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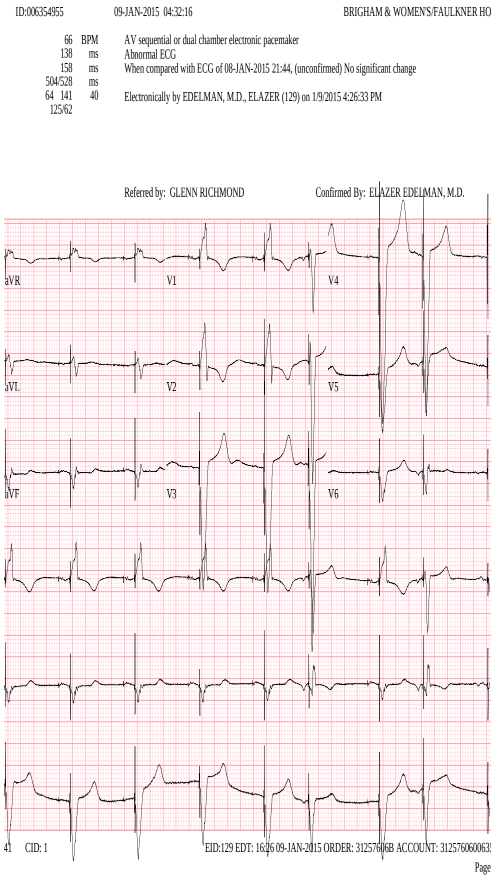


ID:006354955 09-JAN-2015 04:32:16 BRIGHAM & WOMEN'S/FAULKNER HO

66 BPM
138 ms
158 ms
504/528 ms
64 141 40
125/62

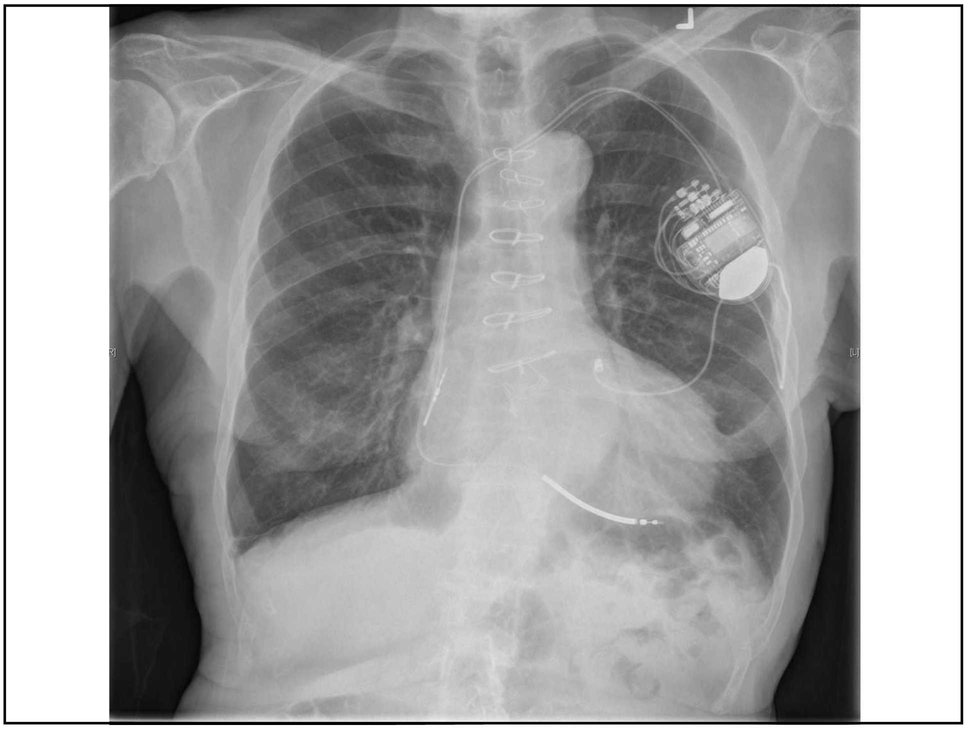
AV sequential or dual chamber electronic pacemaker
Abnormal ECG
When compared with ECG of 08-JAN-2015 21:44, (unconfirmed) No significant change

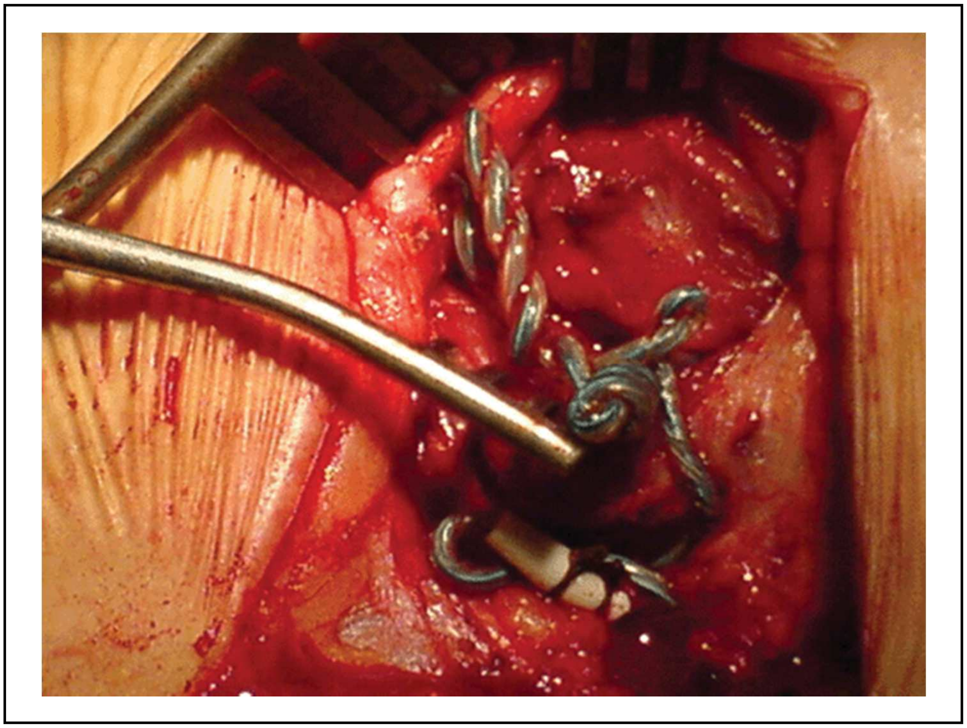
Electronically by EDELMAN, M.D., ELAZER (129) on 1/9/2015 4:26:33 PM

Referred by: GLENN RICHMOND
Confirmed By: ELAZER EDELMAN, M.D.

41 CID: 1 EID:129 EDT: 16:26 09-JAN-2015 ORDER: 31257606B ACCOUNT: 312576060063

Page





PACEMAKER MEDIATED TACHYCARDIA

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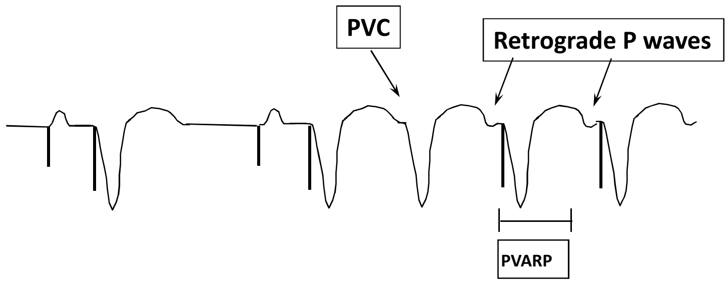
PVC
Retrograde P waves
PVARP

PMT Management

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Prevention

- Program PVARP longer than VA conduction time

Termination

- Tachycardia Termination Algorithm (TTA)
- After 15 consecutive paced ventricular events at EXACTLY the upper rate limit, the 16th ventricular output pulse is dropped
- TTA breaks PMT only at the upper rate limit

PMT Intervention

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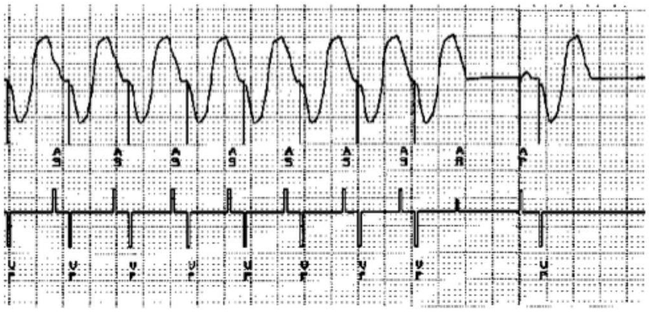
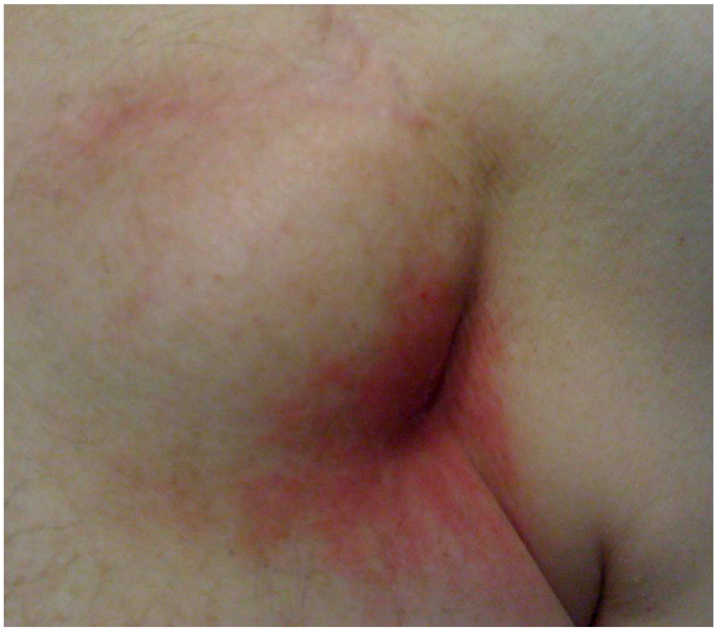
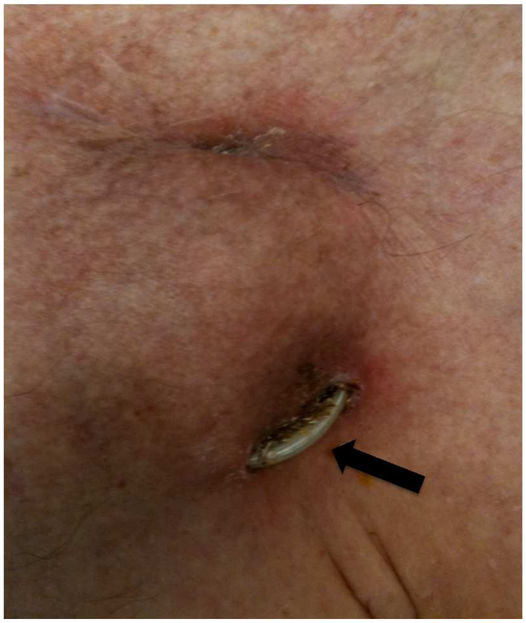
- Designed to interrupt a Pacemaker-Mediated Tachycardia



CIED INFECTION





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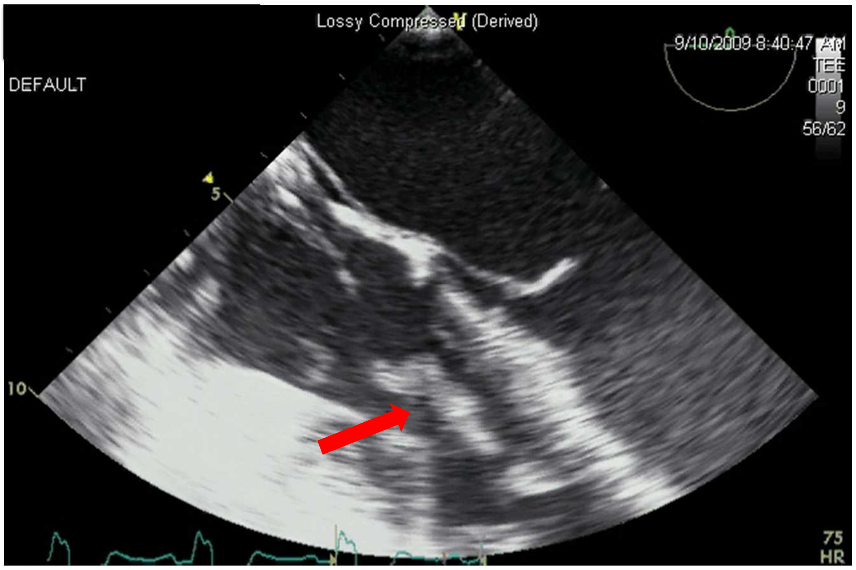
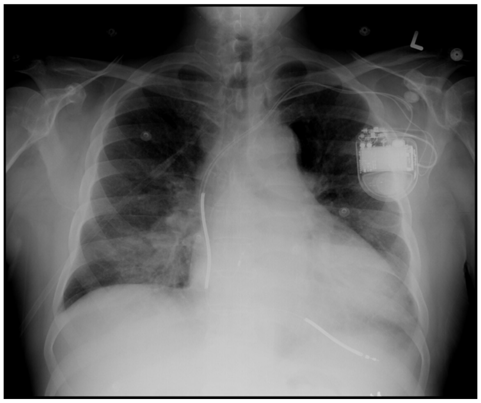

Lossy Compressed (Derived)
9/10/2009 8:40:47 AM
TEE
0001
9
56/62
DEFAULT
5
10
75
HR

Infection Indications for TLE

Indication	Class I Procedure Should be Performed	Class IIa Reasonable to Perform Procedure
Infection	1. Definite CIED infection, e.g. valvular endocarditis, DRE or sepsis. *(LOE: B)* 2. CIED pocket infection, e.g. abscess, erosion or chronic draining sinus. *(LOE: B)* 3. Valvular endocarditis w/o definite lead and/or device involvement. *(LOE: B)* 4. Occult gram-positive bacteremia. *(LOE: B)*	Persistent occult gram-negative bacteremia. *(LOE: B)*

- With expanded device utilization and indications for device therapy, need for lead management from time of implantation has become a necessity
- Device use has increased exponentially over the past decade with more than 4.5 million active devices and more than 1 million new leads implanted annually



Growing Challenge of Lead Management

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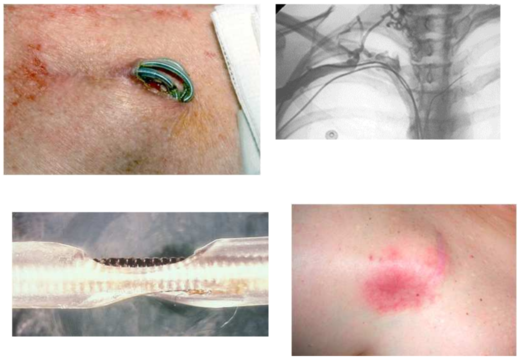
- Growth trends result in more ….
  - Infection
  - Malfunction
  - Upgrade to ICD & Bi-V therapy
  - Venous occlusion



Risk vs. Risk

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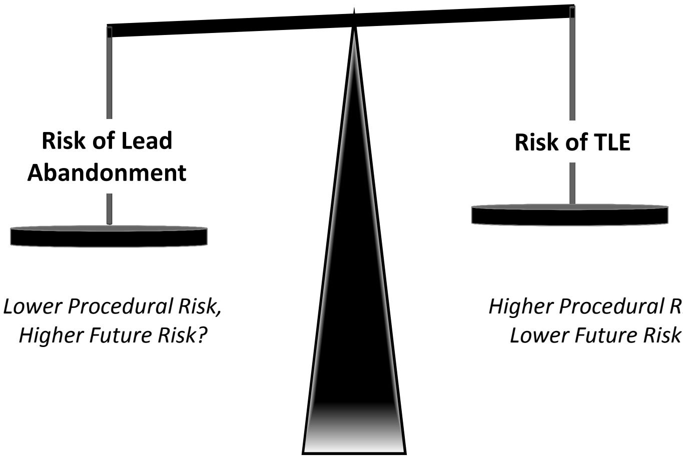


Risk of Lead Abandonment

Lower Procedural Risk, Higher Future Risk?

Risk of TLE

Higher Procedural Risk, Lower Future Risk?

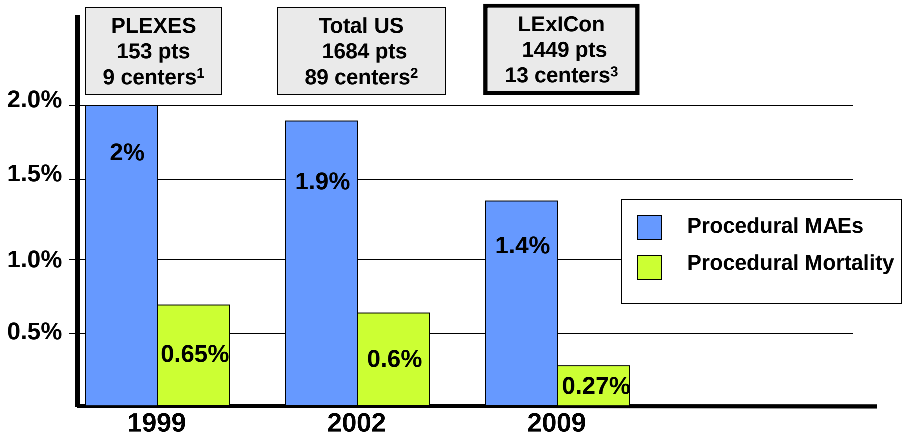
Must Individualize

Risks of Capping/Lead Abandonment

More & older leads for future removal	- Risk of infection increases 2-7% at each device change[1] - Risk of failed lead removal doubles every 3 years[2]
More pocket bulk	- Risk of erosion[3] and infection
More venous lead burden	- Risk of venous thrombosis[3] or occlusion • Prevent access to new leads; right-sided implant - Risk of clotting or SVC syndrome
More tricuspid lead burden	- Risk of increased tricuspid regurgitation[4] and resulting A Fib or right-sided heart failure
Lead-on-lead interaction	- Risk of inappropriate shocks, post traumatic stress disorder or inappropriate pace/sense behavior

1. Wilkoff, Bruce L. , et al. How to treat and identify device infections. *Heart Rhythm*, Vol 4, No 11, 2007, 1467-1470.
2. Byrd, CL, et al. Intravascular extraction of problematic or infected permanent pacemaker leads: 1994-1996. U.S. Extraction Datbase, MED Institute. *PACE* 1999; 22:1348-1357.
3. Bohm, Adam, et al. Complications Due to Abandoned Noninfected Pacemaker Leads. *PACE*, Vol 24, No 12, 2001, 1721-1724.
4. de Cock CC, et al. Long-term outcome of patients with multuiple (> or = 3) noninfected leads: a clinical and echocardiographic study. *PACE*, Vol 23, No 4, 2000, 423-6.

Clinically Proven Safety of Laser Assisted Lead Removal



1. Wilkoff, Bruce, L., et al. Pacemaker Lead Extraction with the Laser Sheath: Results of the Pacing Lead Extraction with Excimer Sheath (PLEXES) Trial. *JACC*, Vol 33, No. 6, May 1999.
2. Byrd, Charles, et al. Clinical Study of the Laser Sheath for Lead Extraction: The Total Experience in the United States. *Journal of Pacing and Electrophysiology*. Vol I25, No. 5, May 2002.
3. Wazni, Oussauma, et al. The LExICon Study: A Multicenter Observational Retrospective Study of Consecutive Laser Lead Extractions. *Heart Rhythm*, Vol 6, Issue 5, Supp May 2009, Ab AB 39-5.

Questions

Question #1

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- A 68-year-old female with a dual chamber ICD is scheduled to undergo elective hemicolectomy. Recent device interrogation reveals no underlying rhythm with 100% atrial and ventricular pacing. Which of the following interventions will be most likely to prevent inappropriate inhibition of pacing by surgical electrocautery?
  - A) Program the defibrillator to "off" mode
  - B) Place a magnet over the device
  - C) Reprogram the pacemaker to an asynchronous mode
  - D) Utilize the electrocautery as close as possible to the generator
  - E) Deliver electrocautery bursts only after each paced beat is delivered

Question #1

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- A 68-year-old female with a dual chamber ICD is scheduled to undergo elective hemicolectomy. Recent device interrogation reveals no underlying rhythm with 100% atrial and ventricular pacing. Which of the following interventions will be most likely to prevent inappropriate inhibition of pacing by surgical electrocautery?
  - A) Program the defibrillator to "off" mode
  - B) Place a magnet over the device
  - C) Reprogram the pacemaker to an asynchronous mode
  - D) Utilize the electrocautery as close as possible to the generator
  - E) Deliver electrocautery bursts only after each paced beat is delivered

---

Question #2

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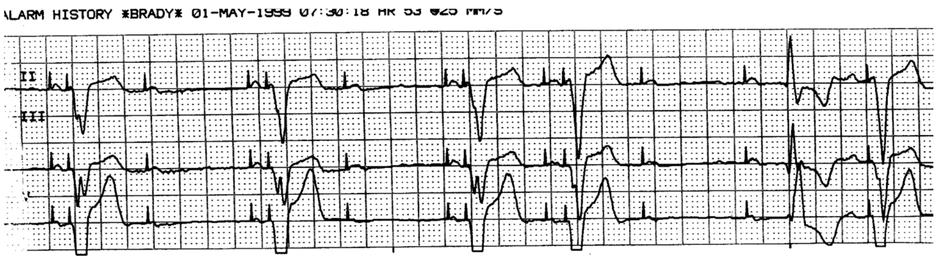
- 35-year-old male lumberjack with cardiac sarcoid and a dual chamber ICD presents with new onset lightheadedness and near-syncope. The following rhythm strip is obtained:



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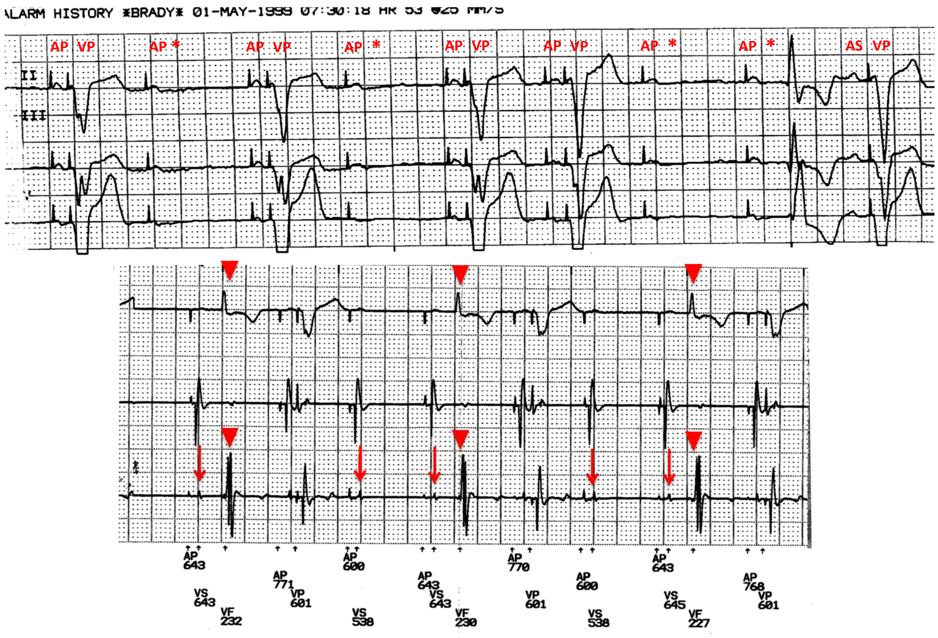
Question #2

- Which of the following explains his symptoms and ECG findings?
  - A) Loss of ventricular capture due to electrolyte abnormalities
  - B) Loss of ventricular capture due to ventricular undersensing
  - C) Loss of ventricular capture due to lead dislodgement
  - D) Loss of ventricular capture due to ventricular oversensing


ALARM HISTORY *BRADY* 01-MAY-1999 07:30:18 HR 53 @25 MM/S
AP VP
AP *
AP VP
AP *
AP VP
AP VP
AP *
AP *
AS VP
II
III
AP 643
VS 643
VF 232
AP 771
VP 601
AP 600
VS 538
AP 643
VS 643
VF 230
AP 770
VP 601
AP 600
VS 538
AP 643
VS 645
VF 227
AP 768
VP 601

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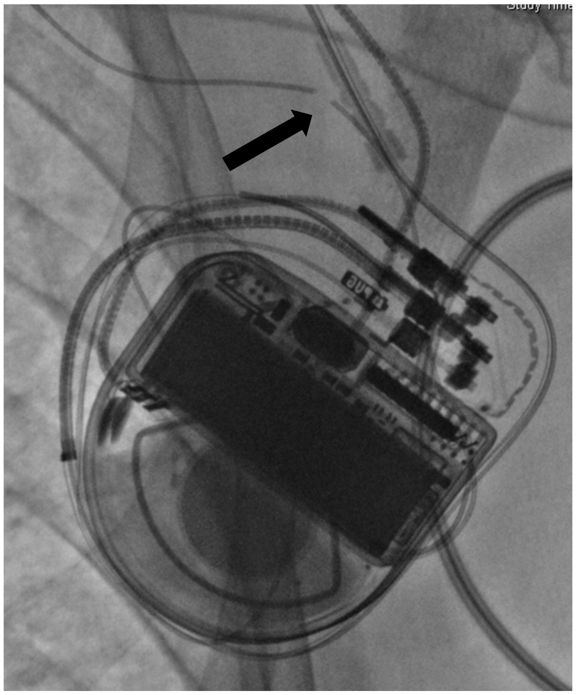
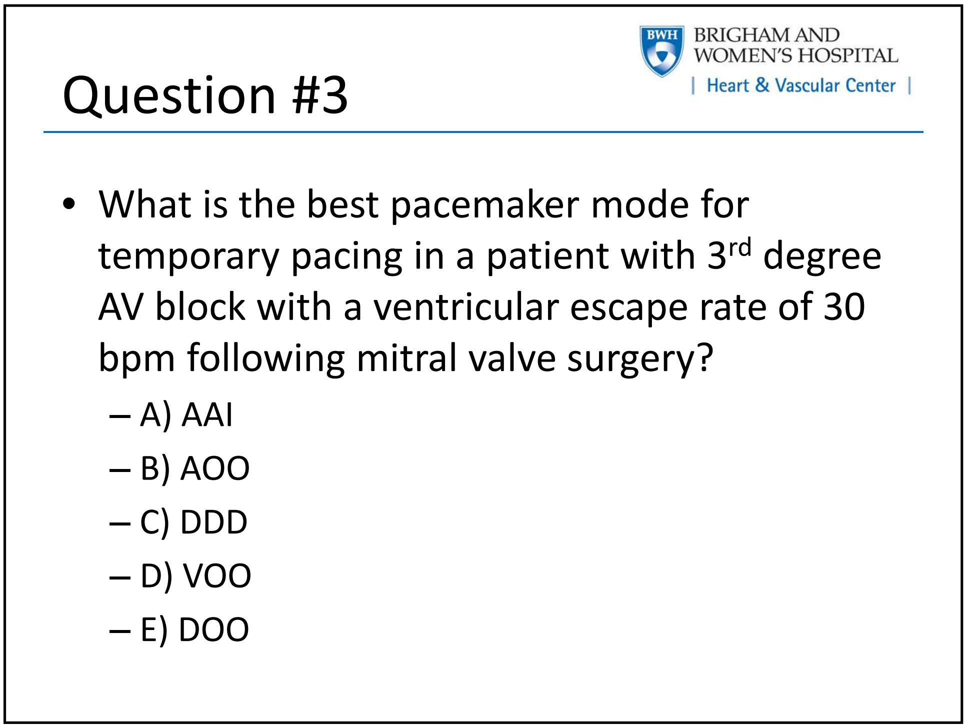
Question #2

- Which of the following explains his symptoms and ECG findings?
  - A) Loss of ventricular capture due to electrolyte abnormalities
  - B) Loss of ventricular capture due to ventricular undersensing
  - C) Loss of ventricular capture due to lead dislodgement
  - D) Loss of ventricular capture due to ventricular oversensing





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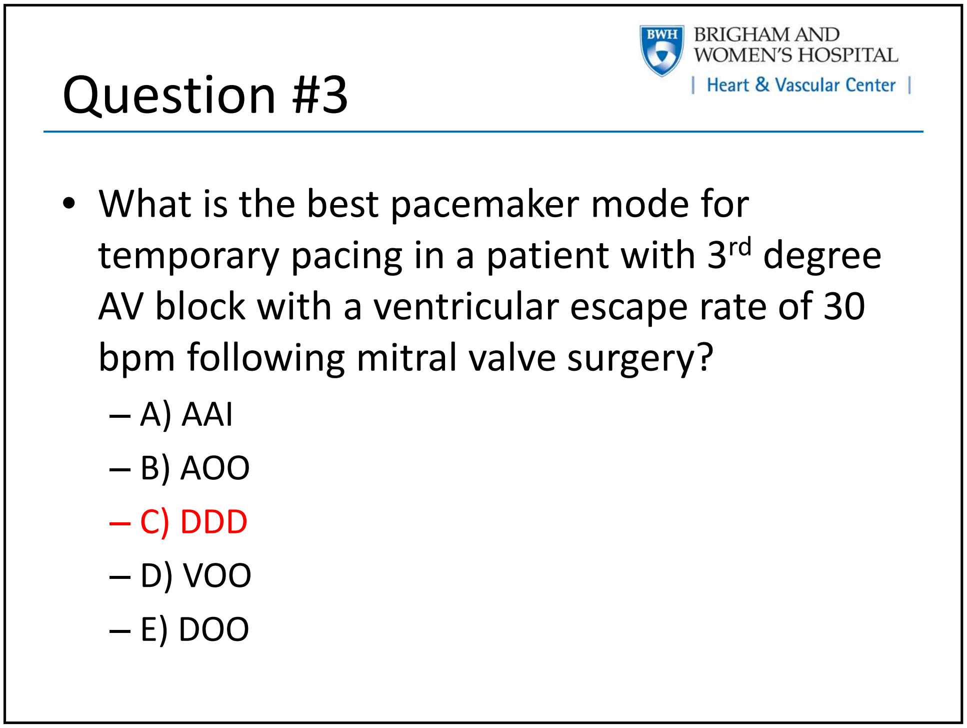
Question #3

- What is the best pacemaker mode for temporary pacing in a patient with 3rd degree AV block with a ventricular escape rate of 30 bpm following mitral valve surgery?
  - A) AAI
  - B) AOO
  - C) DDD
  - D) VOO
  - E) DOO



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Question #3

- What is the best pacemaker mode for temporary pacing in a patient with 3rd degree AV block with a ventricular escape rate of 30 bpm following mitral valve surgery?
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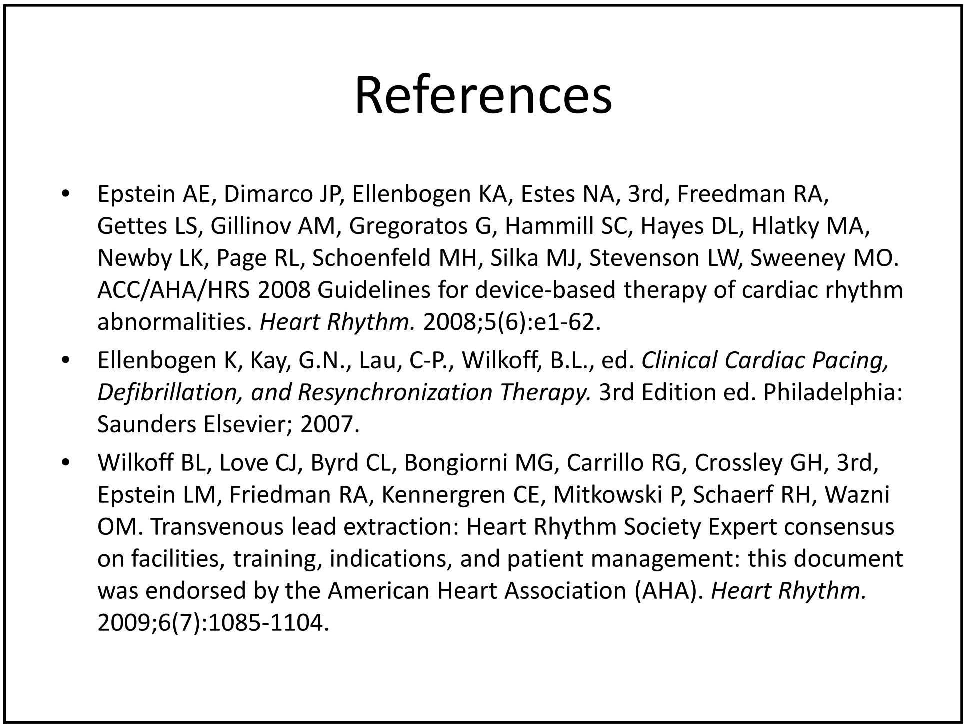
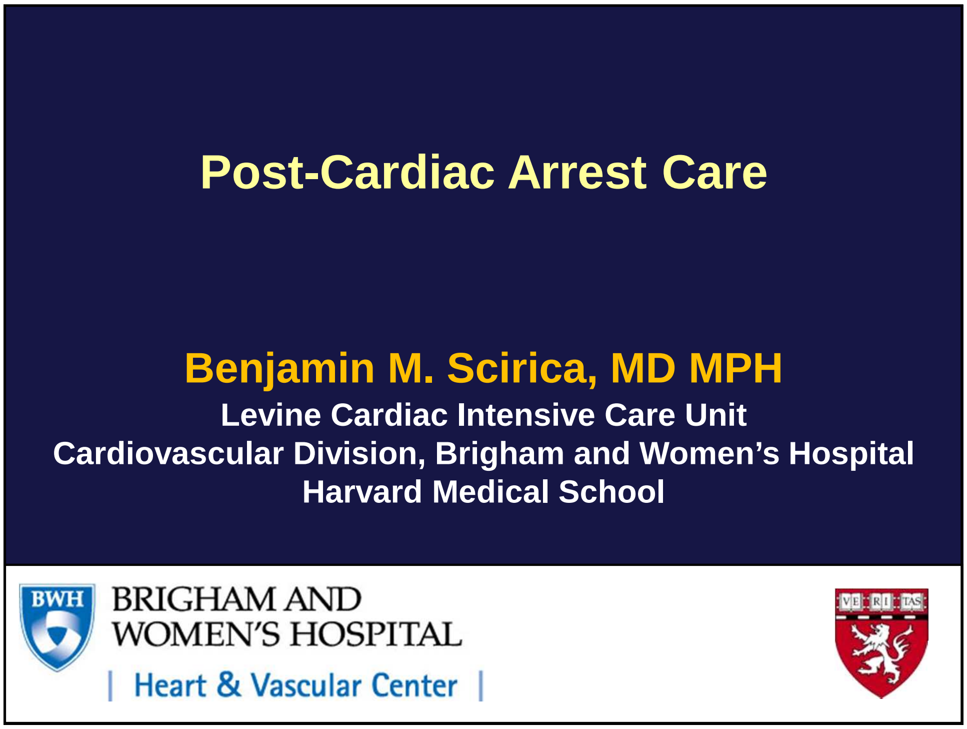
  - B) AOO
  - C) DDD
  - D) VOO
  - E) DOO



References

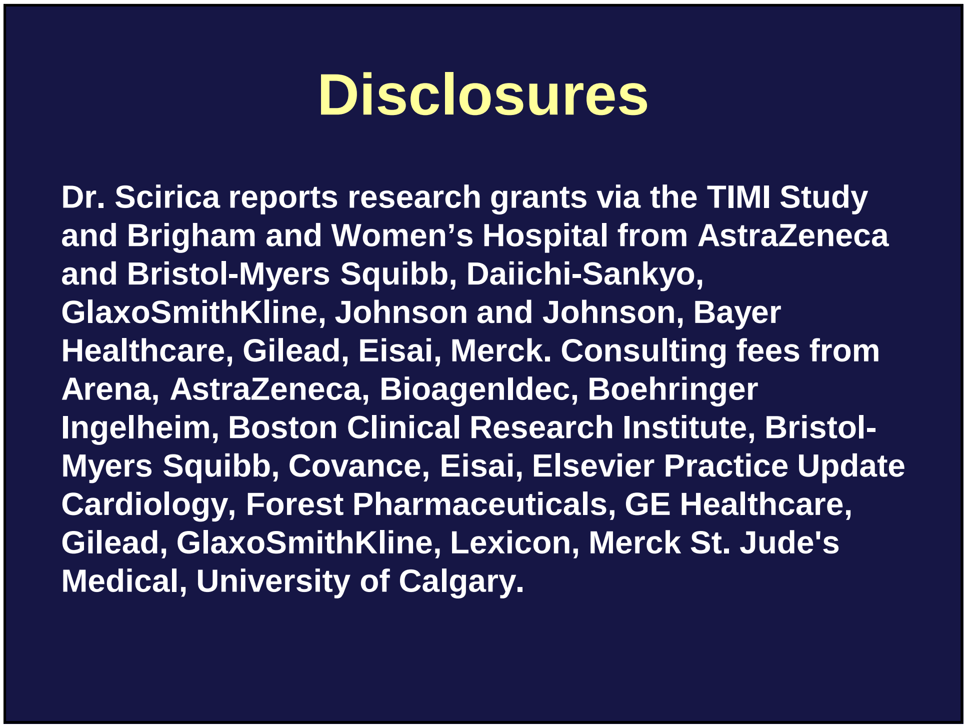
- Epstein AE, Dimarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *Heart Rhythm.* 2008;5(6):e1-62.
- Ellenbogen K, Kay, G.N., Lau, C-P., Wilkoff, B.L., ed. *Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy.* 3rd Edition ed. Philadelphia: Saunders Elsevier; 2007.
- Wilkoff BL, Love CJ, Byrd CL, Bongiorni MG, Carrillo RG, Crossley GH, 3rd, Epstein LM, Friedman RA, Kennergren CE, Mitkowski P, Schaerf RH, Wazni OM. Transvenous lead extraction: Heart Rhythm Society Expert consensus on facilities, training, indications, and patient management: this document was endorsed by the American Heart Association (AHA). *Heart Rhythm.* 2009;6(7):1085-1104.



Post-Cardiac Arrest Care

Benjamin M. Scirica, MD MPH
Levine Cardiac Intensive Care Unit
Cardiovascular Division, Brigham and Women's Hospital
Harvard Medical School

BRIGHAM AND WOMEN'S HOSPITAL
Heart & Vascular Center

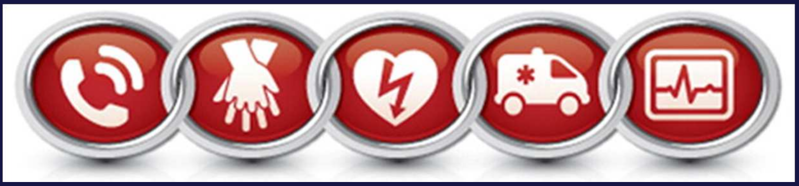


Disclosures

Dr. Scirica reports research grants via the TIMI Study and Brigham and Women's Hospital from AstraZeneca and Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Johnson and Johnson, Bayer Healthcare, Gilead, Eisai, Merck. Consulting fees from Arena, AstraZeneca, BioagenIdec, Boehringer Ingelheim, Boston Clinical Research Institute, Bristol-Myers Squibb, Covance, Eisai, Elsevier Practice Update Cardiology, Forest Pharmaceuticals, GE Healthcare, Gilead, GlaxoSmithKline, Lexicon, Merck St. Jude's Medical, University of Calgary.

Goals of Care after Resuscitation

- Determine and treat cause of arrest
- Minimize brain injury
- Manage cardiovascular dysfunction
- Manage problems that may arise from global ischemia/reperfusion injury



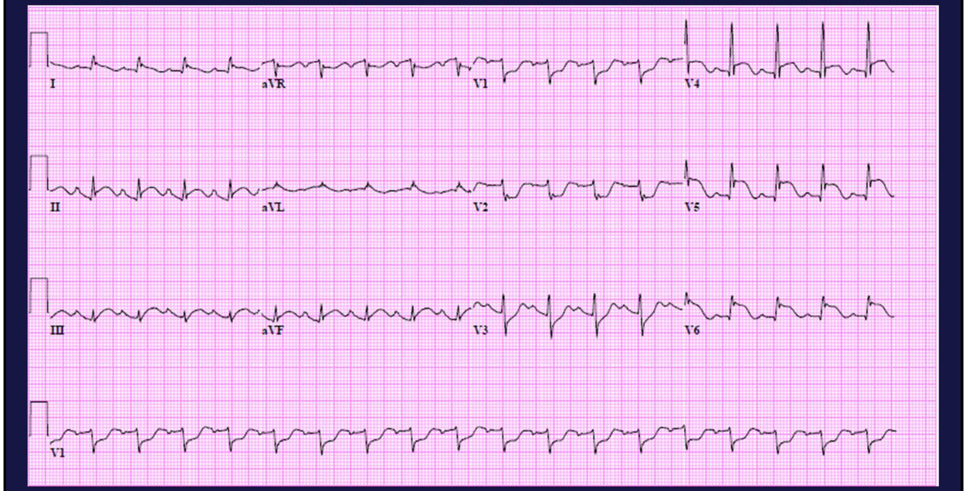
Integrated Post-Cardiac Arrest Care = FIFTH LINK

http://www.heart.org/ECCIntro/Chain-of-Survival_UCM_307516_Article

The Case

- **58 y.o. M who at 11am complained of arm and shoulder pain**
- **Subsequently collapsed at 12:23**
- **Bystander CPR initiated and called 911**
- **EMS arrived and identified VF**
- **Intubated, defibrillated multiple times with return of spontaneous circulation**
- **EKG was notable for an ST-elevation MI**

The Case: ECG


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

The Exam

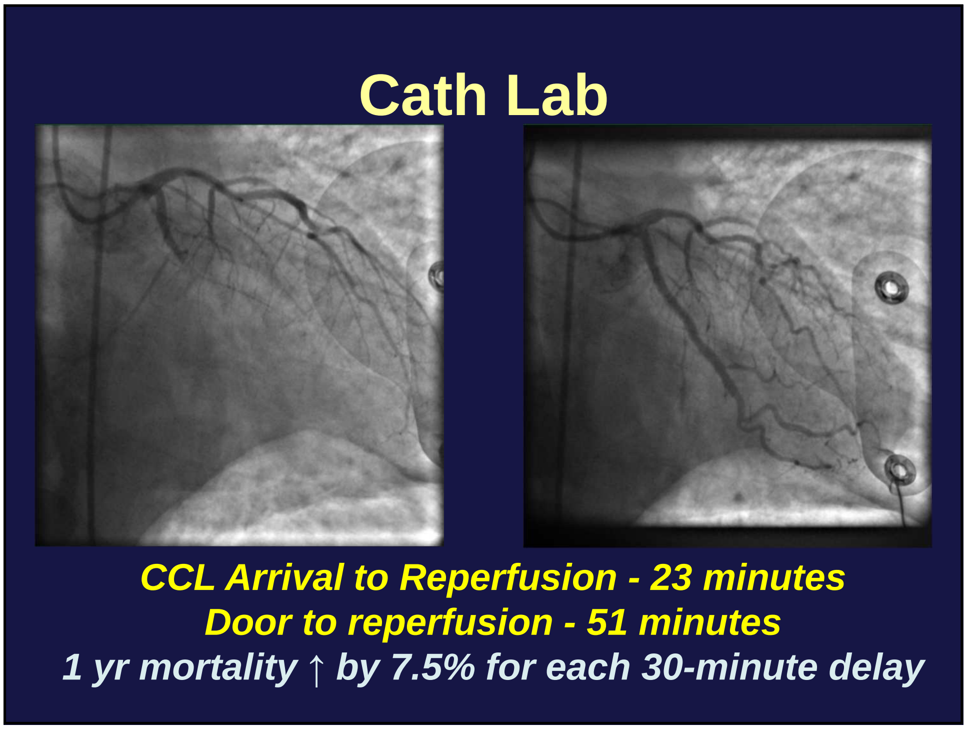
Neurologic Exam:

•Unresponsive to voice or sternal rub.

•Pupils fixed at 8mm, no OCRs, gaze conjugate and midline, face symmetric

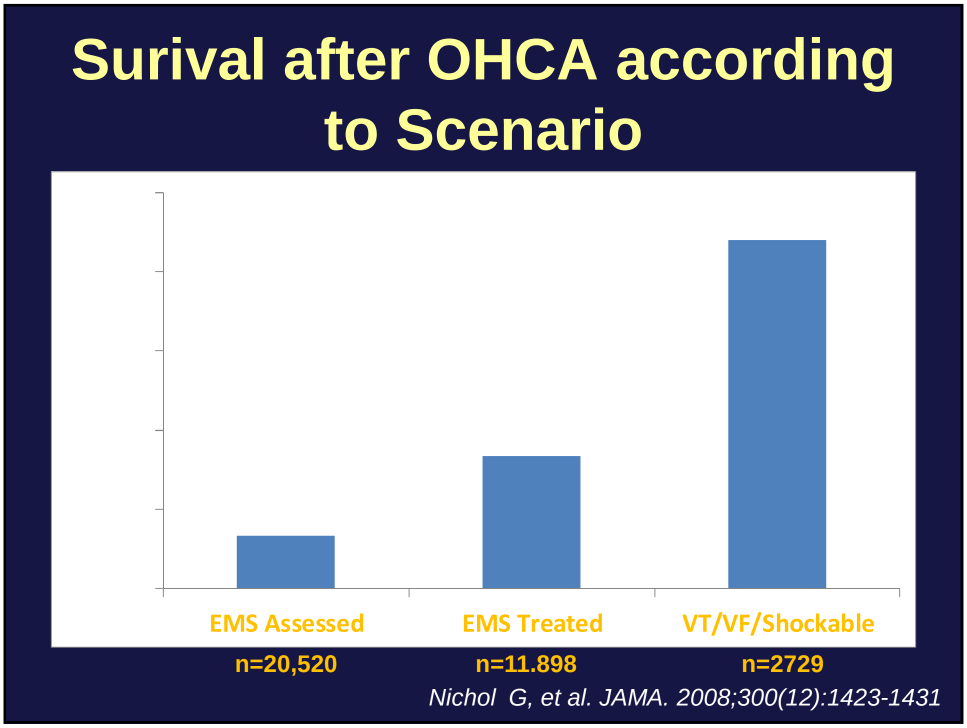
•No spontaneous limb movements or response to painful stimuli

•GCS – 3 (out of 15)



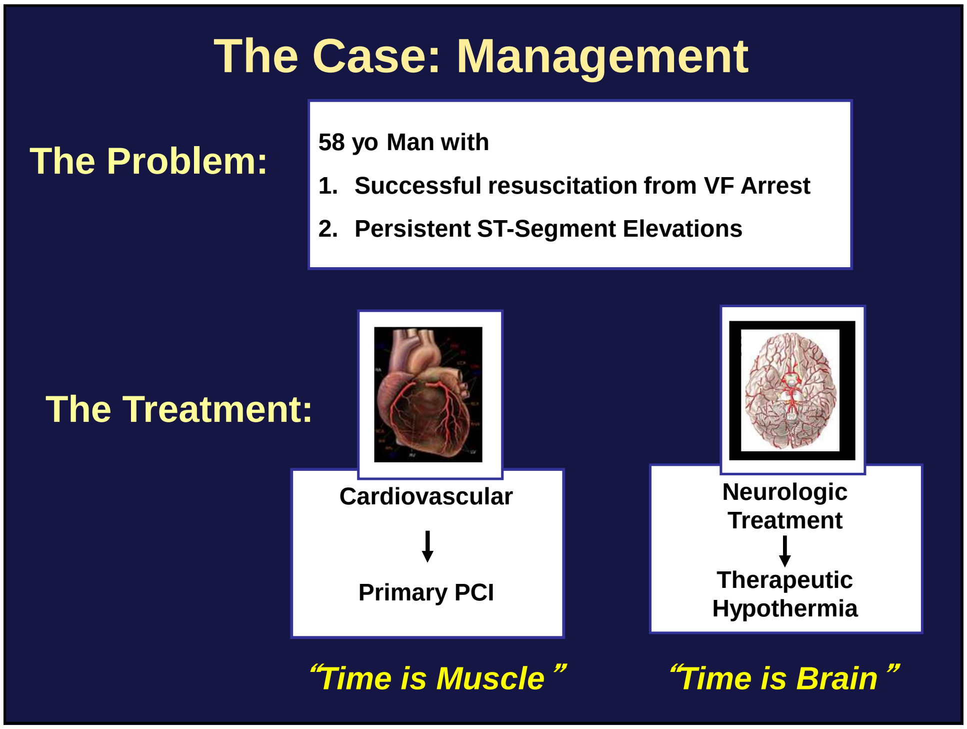
Cath Lab

CCL Arrival to Reperfusion - 23 minutes
Door to reperfusion - 51 minutes
1 yr mortality ↑ by 7.5% for each 30-minute delay



Surival after OHCA according to Scenario

Nichol G, et al. JAMA. 2008;300(12):1423-1431



The Case: Management

The Problem:

58 yo Man with

1. Successful resuscitation from VF Arrest
2. Persistent ST-Segment Elevations

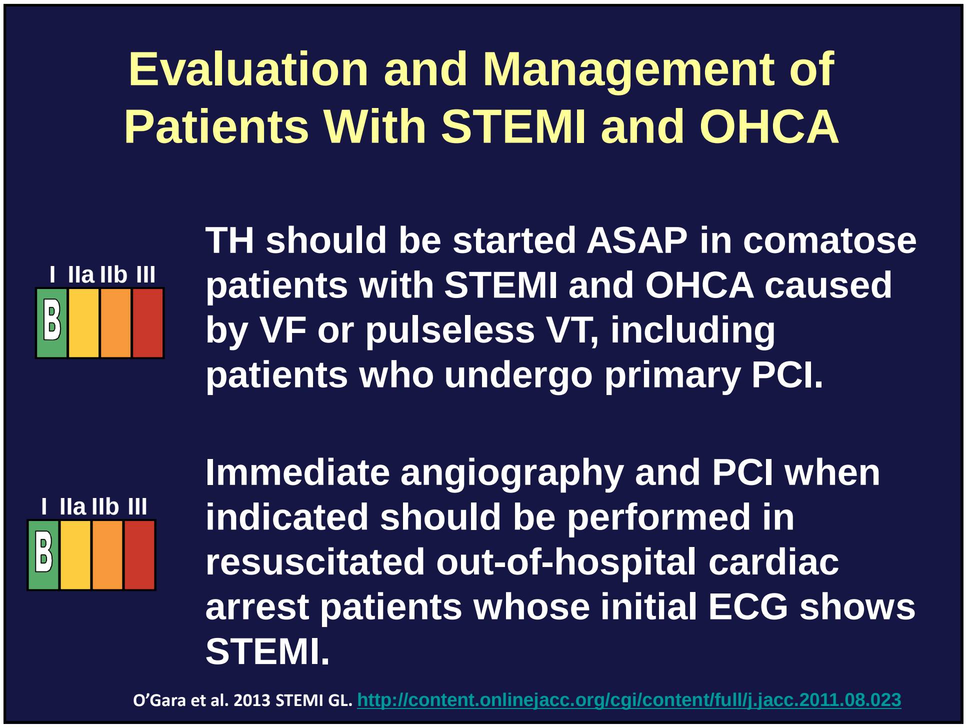
The Treatment:

Cardiovascular
↓
Primary PCI

Neurologic Treatment
↓
Therapeutic Hypothermia

"Time is Muscle"

"Time is Brain"



Evaluation and Management of Patients With STEMI and OHCA

I IIa IIb III
B

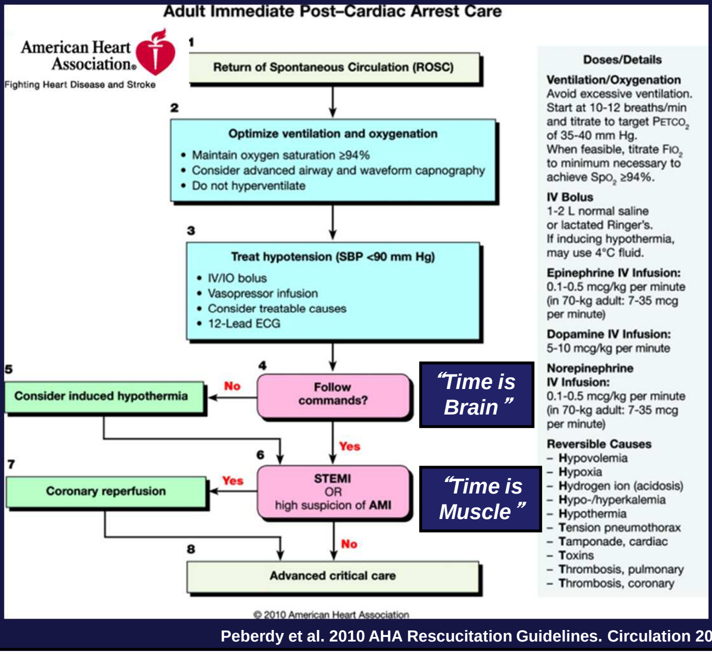
TH should be started ASAP in comatose patients with STEMI and OHCA caused by VF or pulseless VT, including patients who undergo primary PCI.

I IIa IIb III
B

Immediate angiography and PCI when indicated should be performed in resuscitated out-of-hospital cardiac arrest patients whose initial ECG shows STEMI.

O'Gara et al. 2013 STEMI GL. http://content.onlinejacc.org/cgi/content/full/j.jacc.2011.08.023

Post-Cardiac Arrest Care in Adults


Adult Immediate Post–Cardiac Arrest Care
American Heart Association®
Fighting Heart Disease and Stroke
1
Return of Spontaneous Circulation (ROSC)
2
Optimize ventilation and oxygenation
• Maintain oxygen saturation ≥94%
• Consider advanced airway and waveform capnography
• Do not hyperventilate
3
Treat hypotension (SBP <90 mm Hg)
• IV/IO bolus
• Vasopressor infusion
• Consider treatable causes
• 12-Lead ECG
4
Follow commands?
No
5
Consider induced hypothermia
Yes
6
STEMI OR high suspicion of AMI
Yes
7
Coronary reperfusion
No
8
Advanced critical care
"Time is Brain"
"Time is Muscle"
© 2010 American Heart Association

Doses/Details

Ventilation/Oxygenation
Avoid excessive ventilation.
Start at 10-12 breaths/min and titrate to target P_{ETCO_2} of 35-40 mm Hg.
When feasible, titrate F_{IO_2} to minimum necessary to achieve S_{PO_2} ≥94%.

IV Bolus
1-2 L normal saline or lactated Ringer's.
If inducing hypothermia, may use 4°C fluid.

Epinephrine IV Infusion:
0.1-0.5 mcg/kg per minute (in 70-kg adult: 7-35 mcg per minute)

Dopamine IV Infusion:
5-10 mcg/kg per minute

Norepinephrine IV Infusion:
0.1-0.5 mcg/kg per minute (in 70-kg adult: 7-35 mcg per minute)

Reversible Causes
- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Peberdy et al. 2010 AHA Rescucitation Guidelines. Circulation 2010;122:S768-86.

AHA Guidelines 2015

American Heart Association®
Fighting Heart Disease and Stroke

Part 8: Post–Cardiac Arrest Care

2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Recommendations:

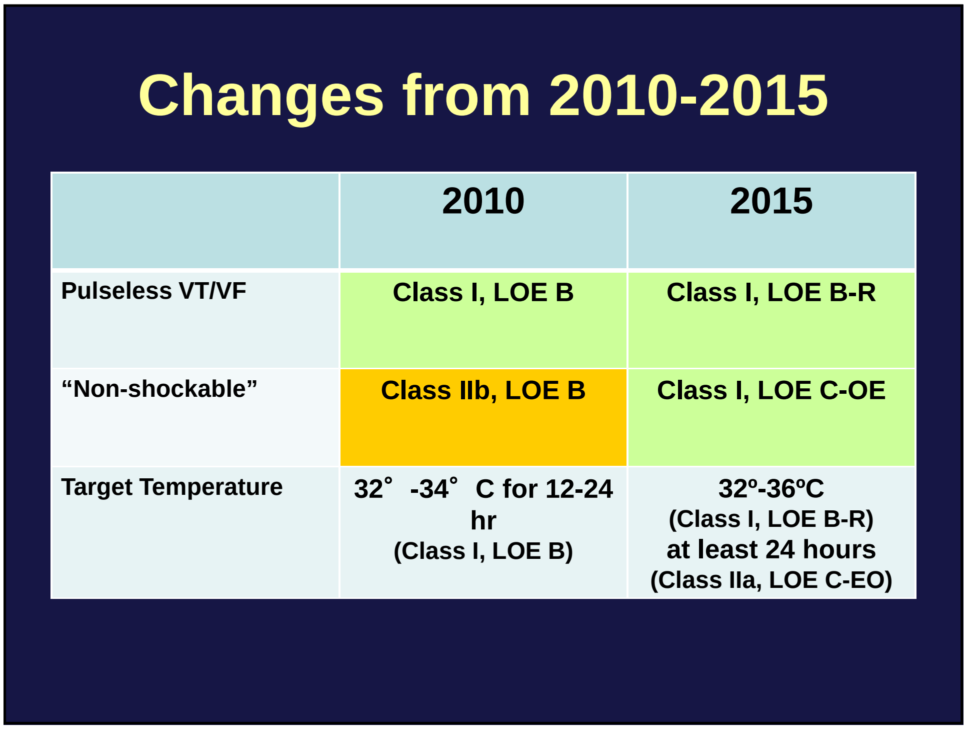
Comatose (ie, *lack of meaningful response to verbal commands*) adult patients with ROSC after cardiac arrest have TTM

- Class I, LOE B-R for VF/pVT OHCA
- Class I, LOE C-EO for non-VF/pVT (ie, "nonshockable") and in-hospital arrest

We recommend selecting and maintaining a constant temperature between 32ºC and 36ºC during TTM

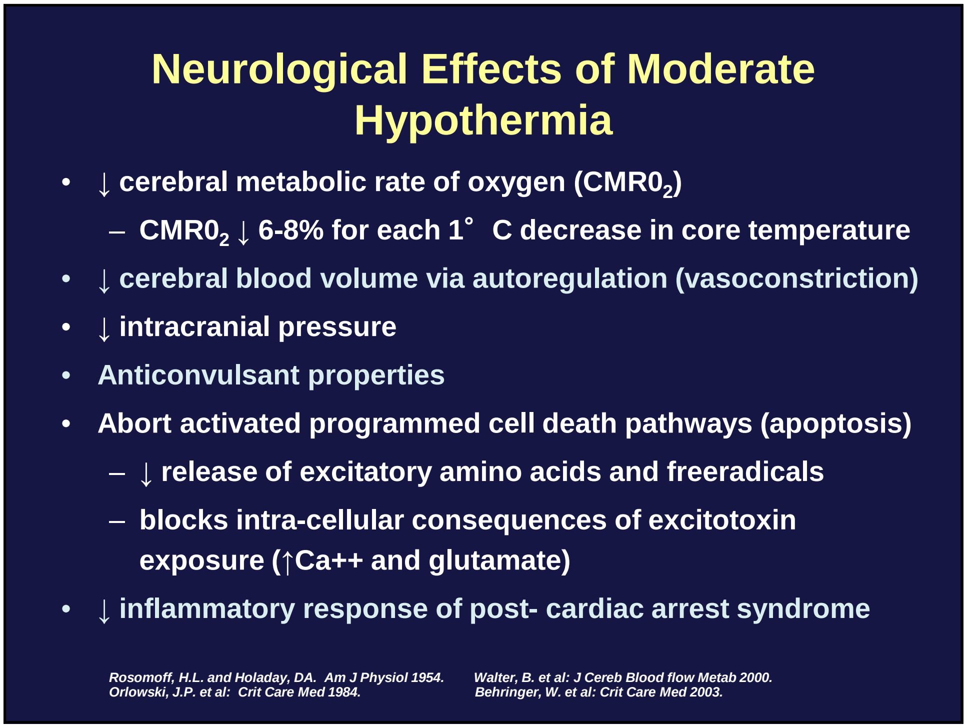
- Class I, LOE B-R

Circulation. 2015;132[suppl 1]:S465–S482.



Changes from 2010-2015

	2010	2015
Pulseless VT/VF	Class I, LOE B	Class I, LOE B-R
"Non-shockable"	Class IIb, LOE B	Class I, LOE C-OE
Target Temperature	32° -34° C for 12-24 hr (Class I, LOE B)	32º-36ºC (Class I, LOE B-R) at least 24 hours (Class IIa, LOE C-EO)



Neurological Effects of Moderate Hypothermia

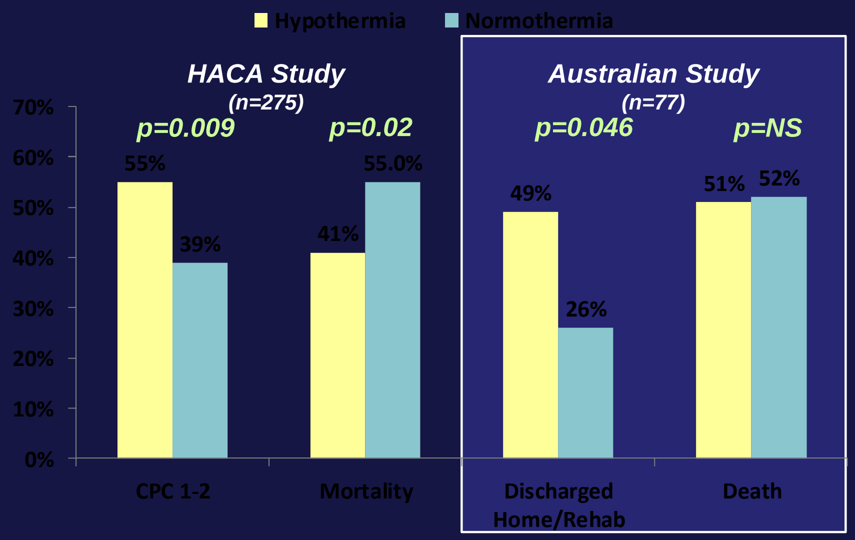
- ↓ cerebral metabolic rate of oxygen (CMR0_2)
  - CMR0_2 ↓ 6-8% for each 1° C decrease in core temperature
- ↓ cerebral blood volume via autoregulation (vasoconstriction)
- ↓ intracranial pressure
- Anticonvulsant properties
- Abort activated programmed cell death pathways (apoptosis)
  - ↓ release of excitatory amino acids and freeradicals
  - blocks intra-cellular consequences of excitotoxin exposure (↑Ca++ and glutamate)
- ↓ inflammatory response of post- cardiac arrest syndrome

Rosomoff, H.L. and Holaday, DA. Am J Physiol 1954.
Orlowski, J.P. et al: Crit Care Med 1984.
Walter, B. et al: J Cereb Blood flow Metab 2000.
Behringer, W. et al: Crit Care Med 2003.

Comparison of Two Landmark Studies

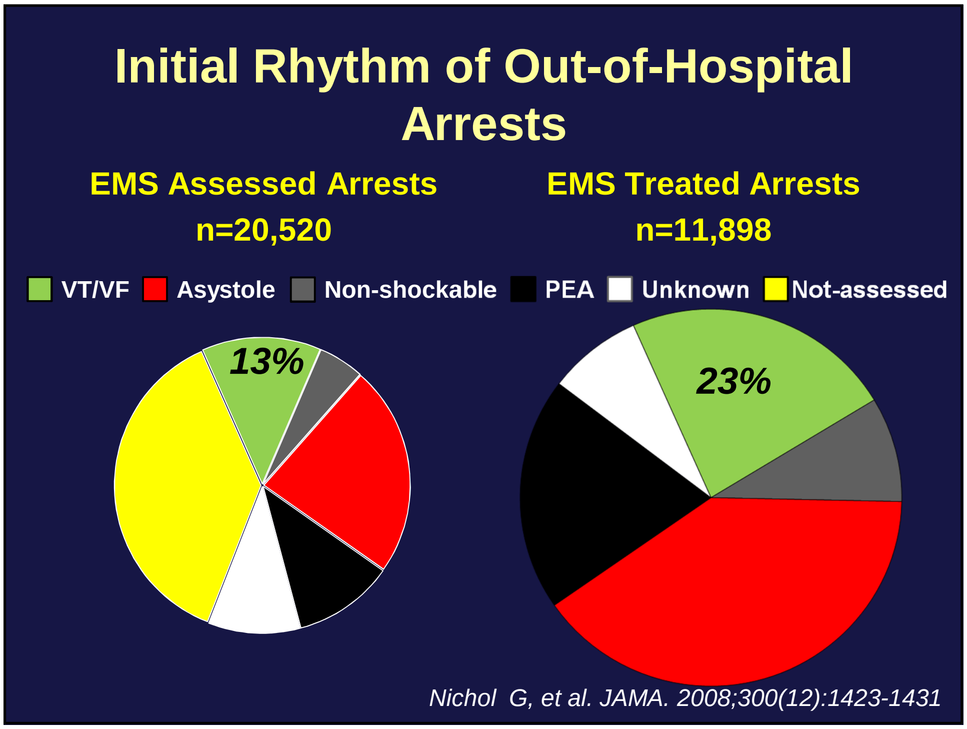
	HACA (n=275)	Australian Study (n=77)
Selection of Therapy	Randomized	Odd/even days
Vent. Fibrillation	92%	100%
Window to cool	1.6 hrs	2 hrs
Target temp	32-34	33
Duration of hypothermia	24 hrs	12 hrs
Time to target temp	8 hours	2.5 hours
Rewarming	Passive over 8 hrs	Active over 6 hours
Follow-up	6 months	D/C
Primary Endpoint	"Favorable" neuro recovery at 6m (CPC 1-2)	"Good" neuro recovery at D/C (D/c home or rehab)

Therapeutic Hypothermia: Clinical Outcomes



HACA, NEJM 2002;346(8):549-556.

Bernard et al. NEJM 2002;346(8) 557-563.

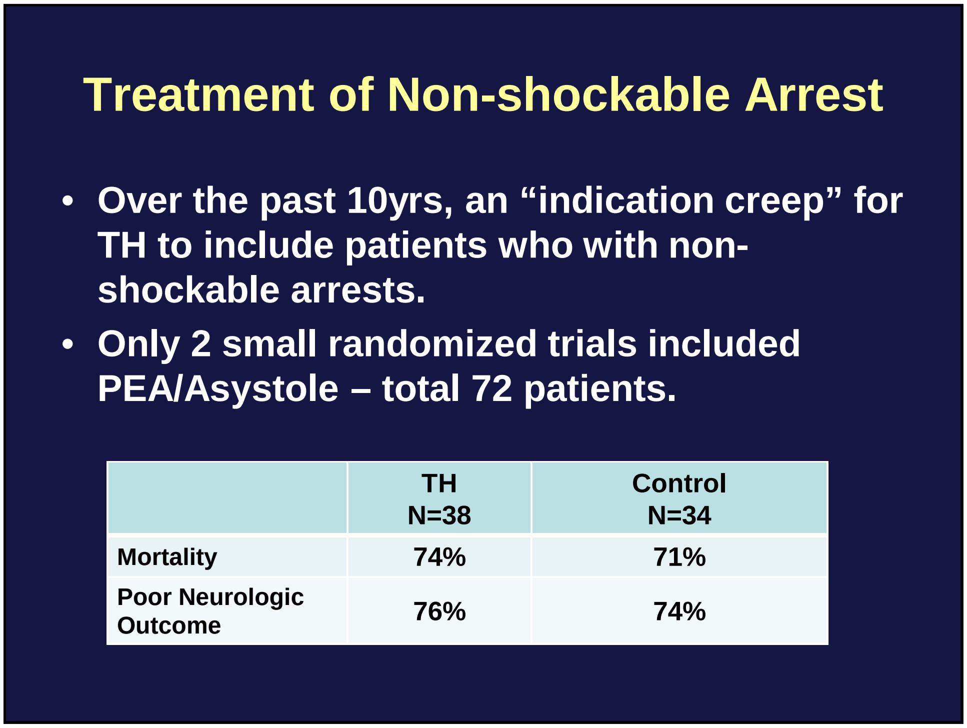


Initial Rhythm of Out-of-Hospital Arrests

EMS Assessed Arrests
n=20,520

EMS Treated Arrests
n=11,898

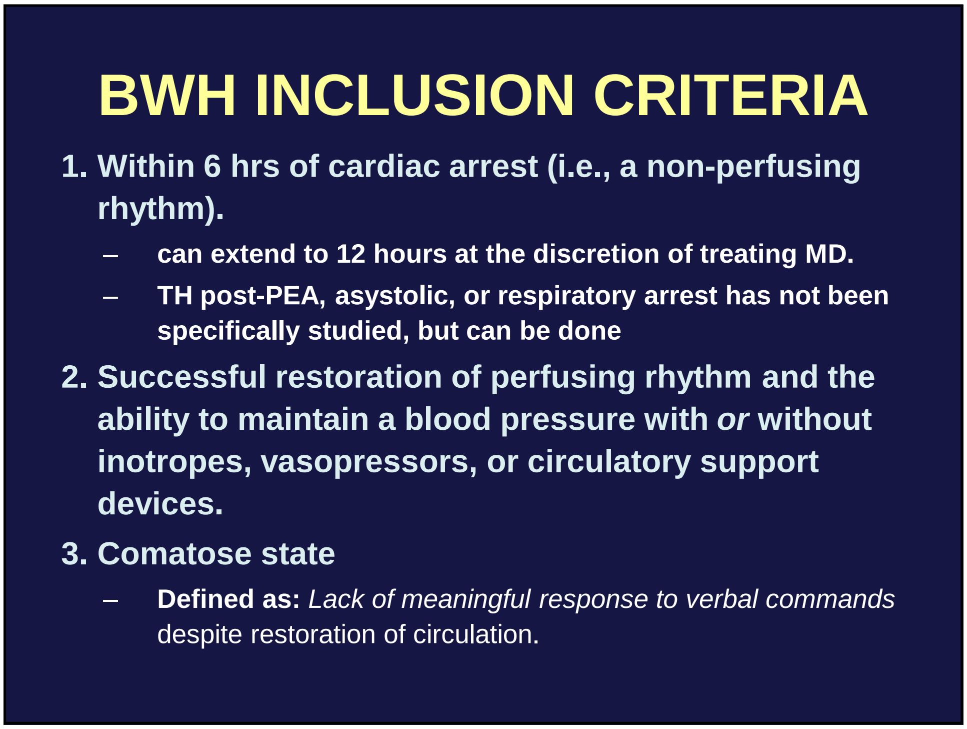
Nichol G, et al. JAMA. 2008;300(12):1423-1431



Treatment of Non-shockable Arrest

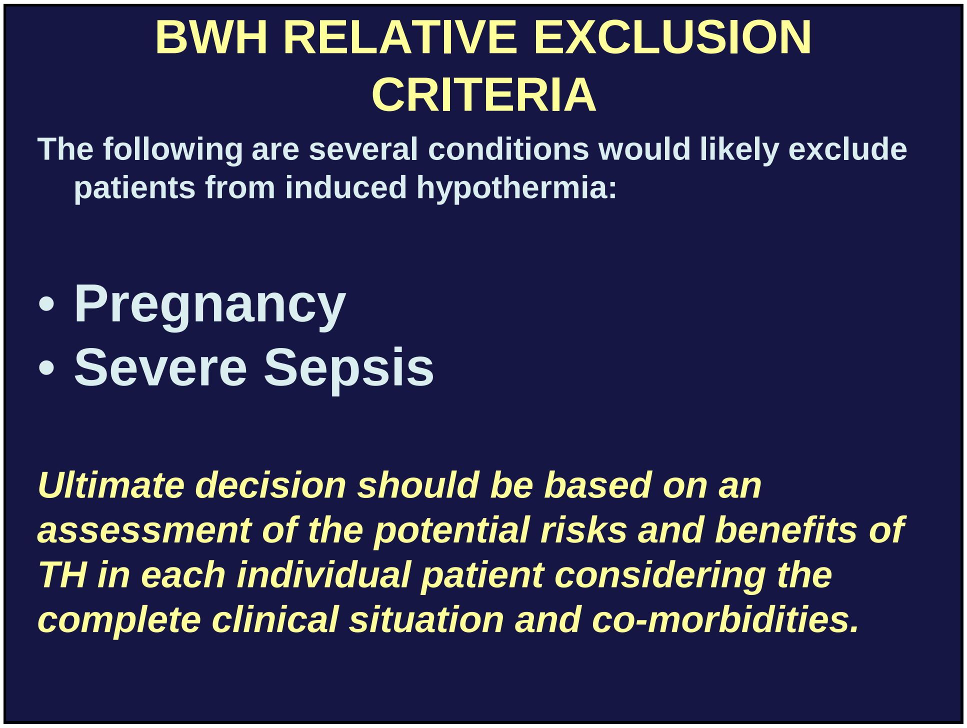
- Over the past 10yrs, an "indication creep" for TH to include patients who with non-shockable arrests.
- Only 2 small randomized trials included PEA/Asystole – total 72 patients.

	TH N=38	Control N=34
Mortality	74%	71%
Poor Neurologic Outcome	76%	74%



BWH INCLUSION CRITERIA

1. Within 6 hrs of cardiac arrest (i.e., a non-perfusing rhythm).
   - can extend to 12 hours at the discretion of treating MD.
   - TH post-PEA, asystolic, or respiratory arrest has not been specifically studied, but can be done
2. Successful restoration of perfusing rhythm and the ability to maintain a blood pressure with *or* without inotropes, vasopressors, or circulatory support devices.
3. Comatose state
   - **Defined as:** *Lack of meaningful response to verbal commands* despite restoration of circulation.



BWH RELATIVE EXCLUSION CRITERIA

The following are several conditions would likely exclude patients from induced hypothermia:

- Pregnancy
- Severe Sepsis

Ultimate decision should be based on an assessment of the potential risks and benefits of TH in each individual patient considering the complete clinical situation and co-morbidities.

MODIFYING COMORBIDITIES

The following list contains several conditions would likely exclude patients from induced hypothermia:

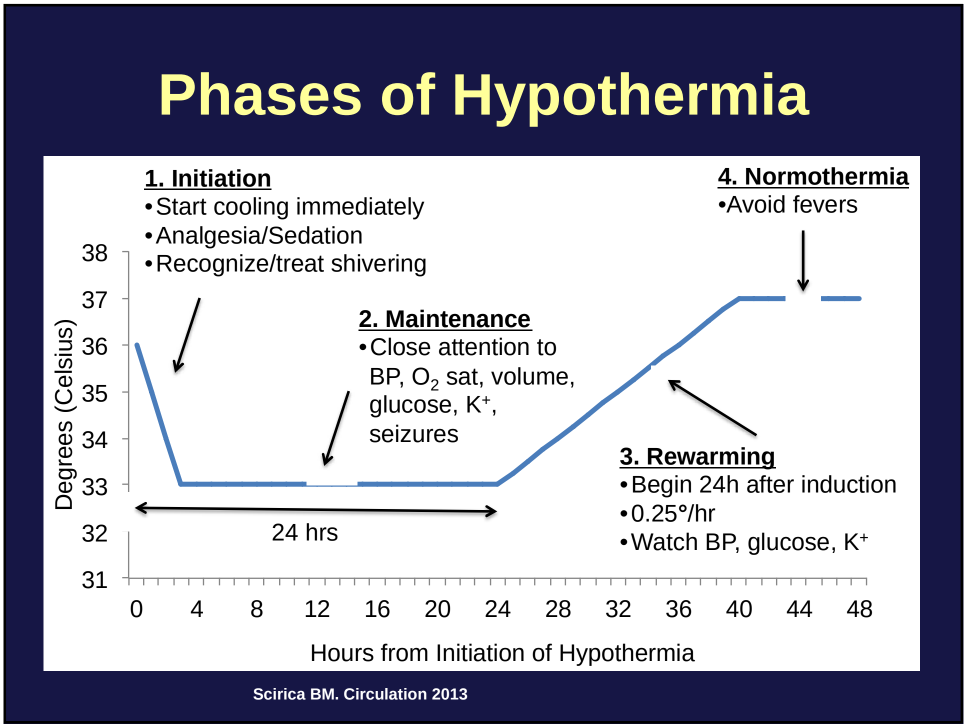
Do any of the following exist:

- Recent Head Trauma
- Clinically significant bleeding/high risk of bleeding
- Major surgery within prior 14 days
- Refractory Hypotension

If yes, consider Targeted Temperature Management with goal 36° C.

No need for head CT before starting TH

Phases of Hypothermia



1. Initiation
- Start cooling immediately
- Analgesia/Sedation
- Recognize/treat shivering

2. Maintenance
- Close attention to BP, O$_2$ sat, volume, glucose, K$^+$, seizures

3. Rewarming
- Begin 24h after induction
- 0.25°/hr
- Watch BP, glucose, K$^+$

4. Normothermia
- Avoid fevers

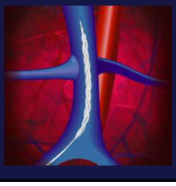
Scirica BM. Circulation 2013

How to Cool - 2017

- Cold saline (4º C) – 2 liters

- Ice bags
- Standard cooling blankets
- Gastric or bladder lavage

- Specialized surface cooling devices
  - Arctic Sun (Medivance)
  - Gaymar Rap-R-Round



- Intravascular Cooling Catheters
  - Innercool (Philips)
  - Alsius (Zoll)

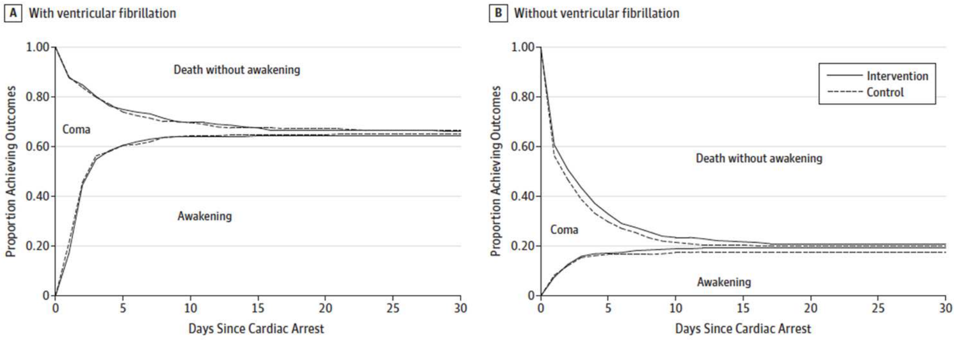
Original Investigation

Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest

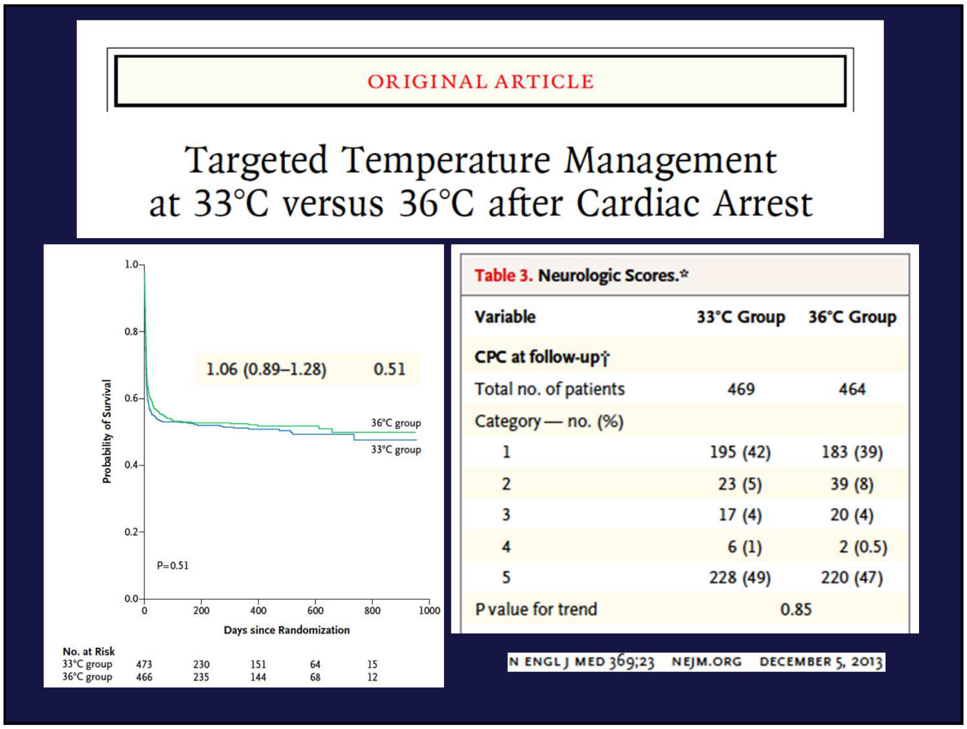
A Randomized Clinical Trial

1359 Patients
Intervention: 2 L of 4C NS as soon as possible following ROSC

At the cost of:
↑ re-arrest (26% v. 21%, p=0.008)
↑ Pulmonary edema (41% v. 30%, p<0.001)



JAMA. 2014;311(1):45-52. doi:10.1001/jama.2013.282173



ORIGINAL ARTICLE

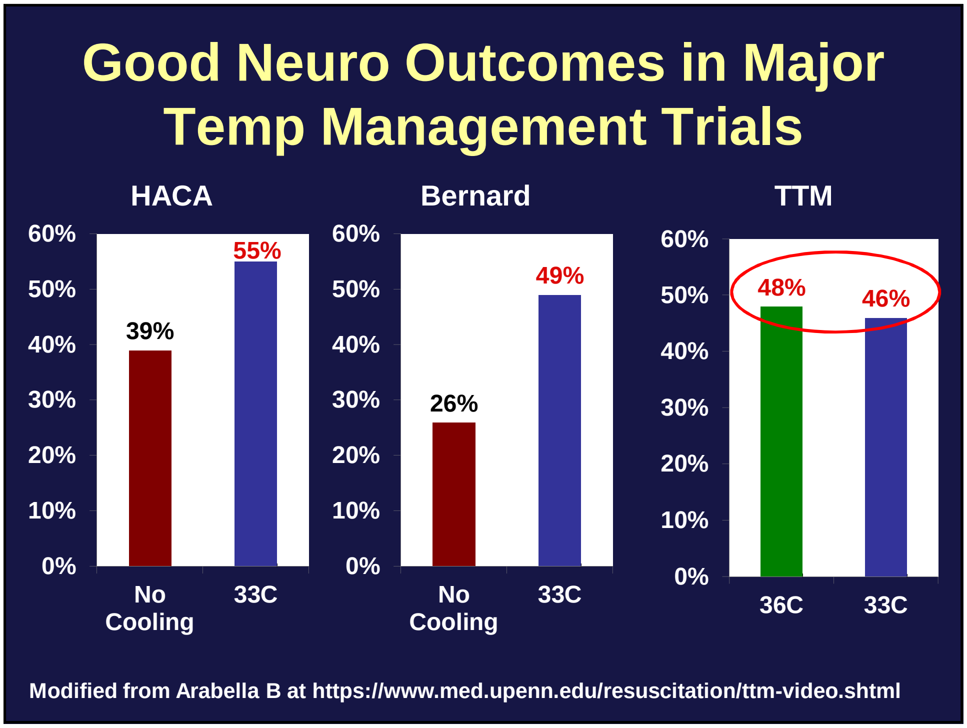
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

1.0
0.8
0.6
0.4
0.2
0.0
Probability of Survival
1.06 (0.89–1.28)
0.51
36°C group
33°C group
P=0.51
0
200
400
600
800
1000
Days since Randomization
No. at Risk
33°C group 473 230 151 64 15
36°C group 466 235 144 68 12

Table 3. **Neurologic Scores.***

Variable	**33°C Group**	**36°C Group**
CPC at follow-up†		
Total no. of patients	469	464
Category — no. (%)		
1	195 (42)	183 (39)
2	23 (5)	39 (8)
3	17 (4)	20 (4)
4	6 (1)	2 (0.5)
5	228 (49)	220 (47)
P value for trend	0.85	

N ENGL J MED 369;23 NEJM.ORG DECEMBER 5, 2013

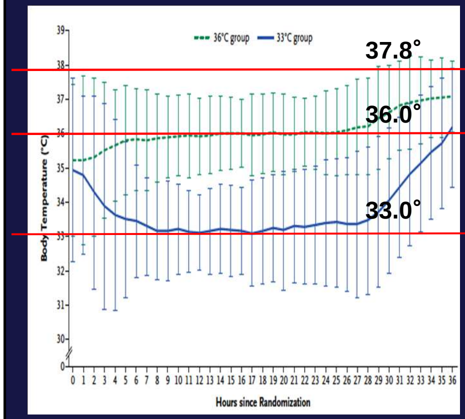


Good Neuro Outcomes in Major Temp Management Trials

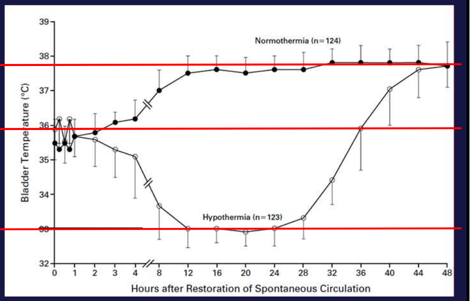
Modified from Arabella B at https://www.med.upenn.edu/resuscitation/ttm-video.shtml

TTM Trial in Context with Prior Studies

TTM Trial



HACA Trial



- *TTM Trial does not test same hypothesis and HACA/Bernard Trial*
- *36° is very much "active" temperature management*

Modified from Arabella B at https://www.med.upenn.edu/resuscitation/ttm-video.shtml

---

BWH Recommendations based on TTM Trial

Given that:

•TTM Trial was neutral (neither harm nor benefit)

• Cooling to 33° C based on animal models and 2 RCTs

•Poor prognostic tools at time of arrest

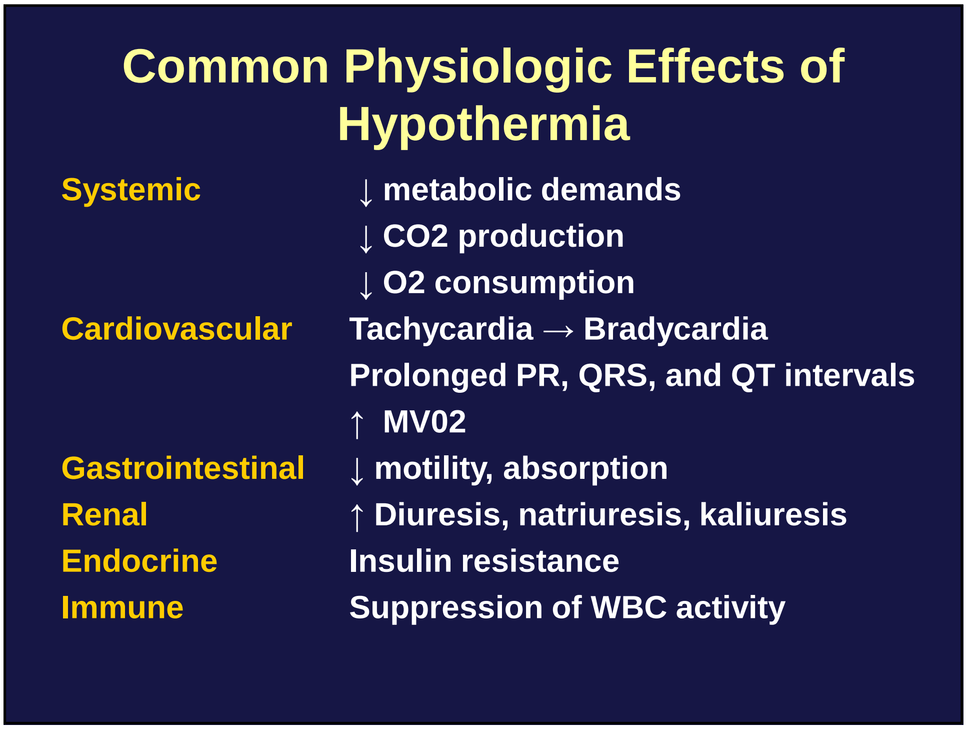
•There is only 1 chance for neuroprotective therapy (immediately post arrest)

BWH Recommendations

•Target temp goal should remain 33° C

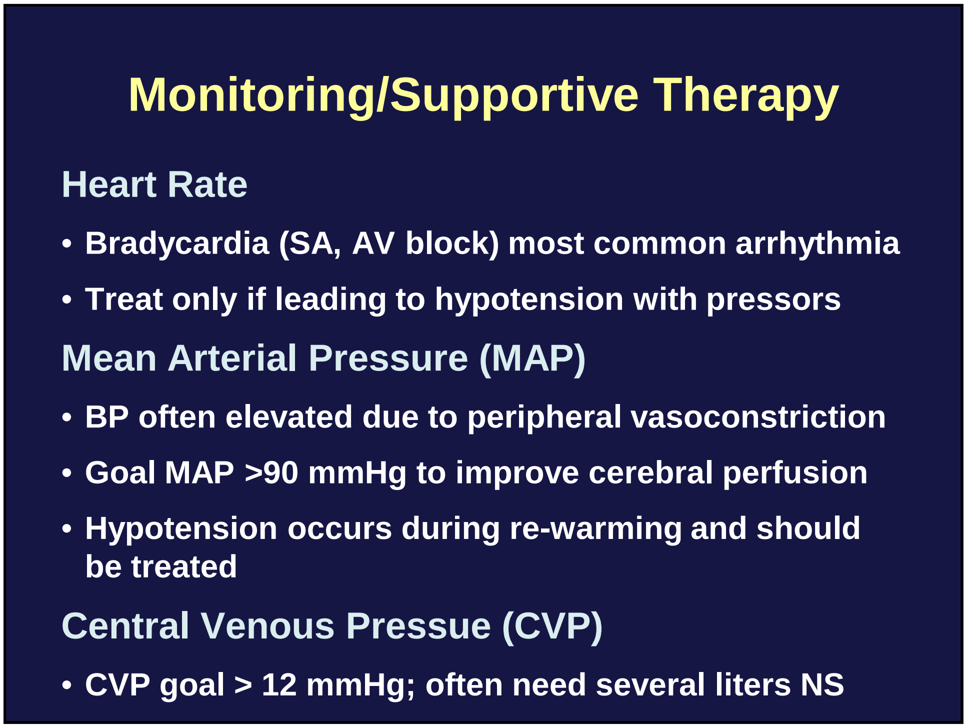
•TTM trial allows flexibility to aim for goal between 33-36° C

Modified from Arabella B at https://www.med.upenn.edu/resuscitation/ttm-video.shtml



Common Physiologic Effects of Hypothermia

Systemic	↓ metabolic demands ↓ CO2 production ↓ O2 consumption
Cardiovascular	Tachycardia → Bradycardia Prolonged PR, QRS, and QT intervals ↑ MV02
Gastrointestinal	↓ motility, absorption
Renal	↑ Diuresis, natriuresis, kaliuresis
Endocrine	Insulin resistance
Immune	Suppression of WBC activity



Monitoring/Supportive Therapy

Heart Rate

- Bradycardia (SA, AV block) most common arrhythmia
- Treat only if leading to hypotension with pressors

Mean Arterial Pressure (MAP)

- BP often elevated due to peripheral vasoconstriction
- Goal MAP >90 mmHg to improve cerebral perfusion
- Hypotension occurs during re-warming and should be treated

Central Venous Pressue (CVP)

- CVP goal > 12 mmHg; often need several liters NS

Sedation/Analgesia/NMBA

Sedation

- Goal sedation level of RASS -4 to -5
- Regardless of RASS level, sedatives should be initiated

Analgesic Agents

- Patients should receive low dose, infusion of an analgesic agent

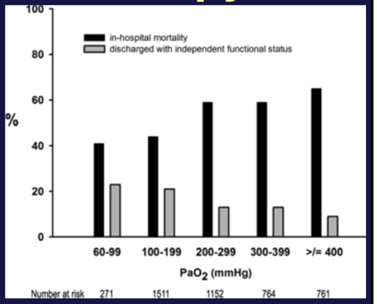
NMBA

- Not recommended empirically in all patients.
- If persistent shivering, then bolus or continuous infusion needed, in particular during induction

Monitoring/Supportive Therapy

Oxygenation

- Goal sat - 94-96%
- ↓FI02 ASAP to avoid supra-physiologic PaO2



Circulation. 2011;123:2717-2722.)

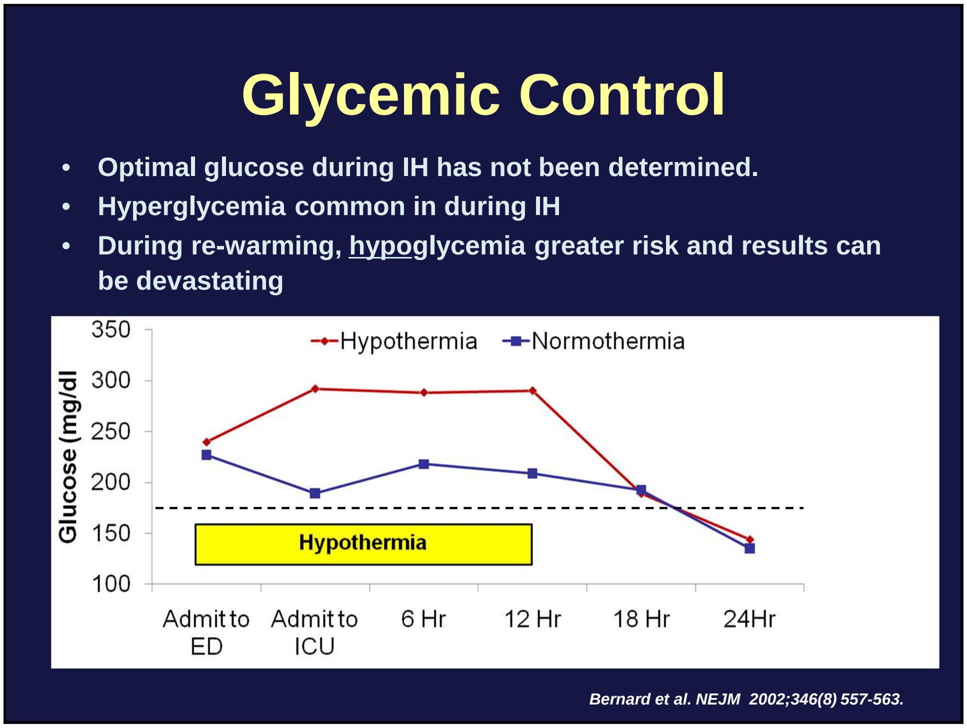
Ventilation

- Intubated with full ventilatory support
- Avoid hyperventilation or hypoventilation
- Ventilator-Associated Pneumonia (VAP) prophylaxis

Monitoring/Supportive Therapy

Infection

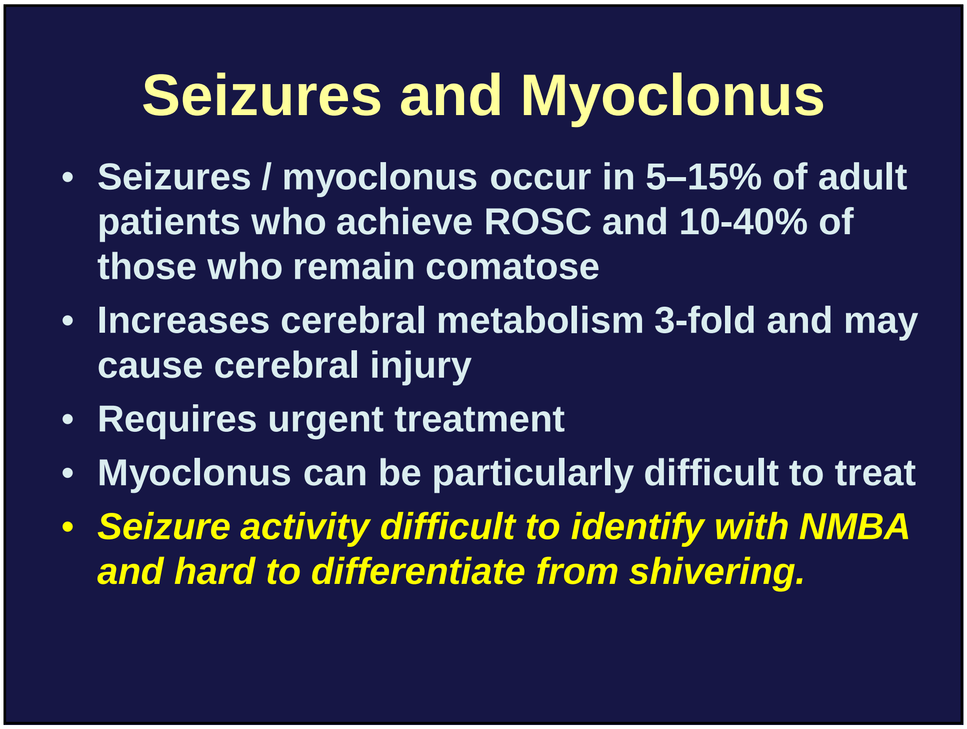
- Common post-arrest (~2/3 of pts)
- Pneumonia most common, followed by blood stream/catheter infection
- G neg. and S. Aureus most common pathogens
- Good news, infection itself not associated with worse outcomes
- *Recommendation* – Early, broad, and aggressive antibiotics Rx at 1st suspicion of infection



Glycemic Control

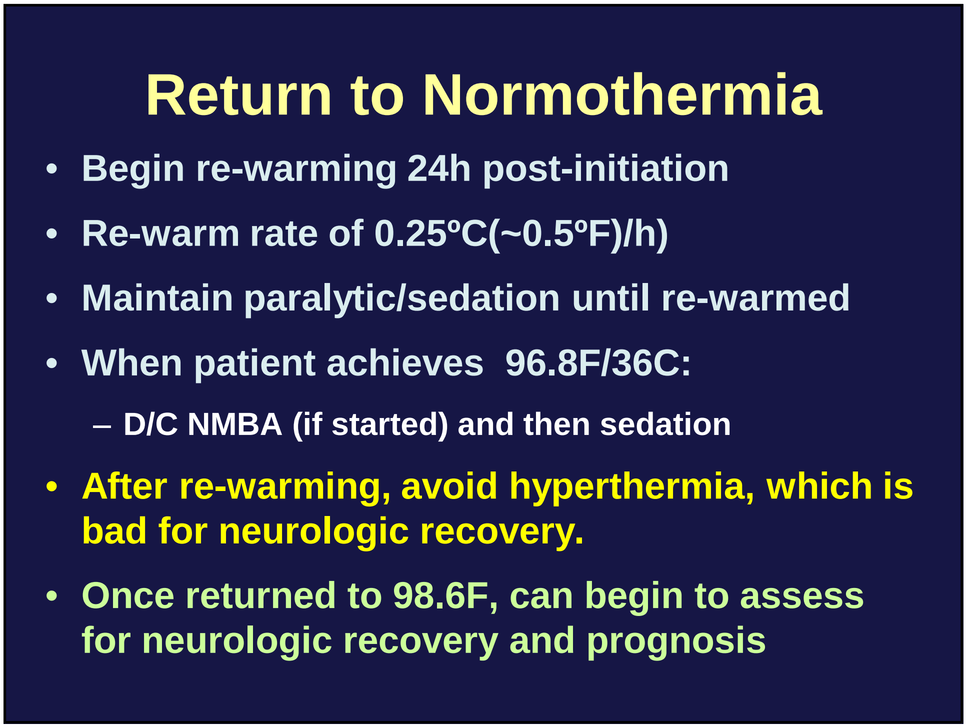
- Optimal glucose during IH has not been determined.
- Hyperglycemia common in during IH
- During re-warming, hypoglycemia greater risk and results can be devastating

Bernard et al. NEJM 2002;346(8) 557-563.



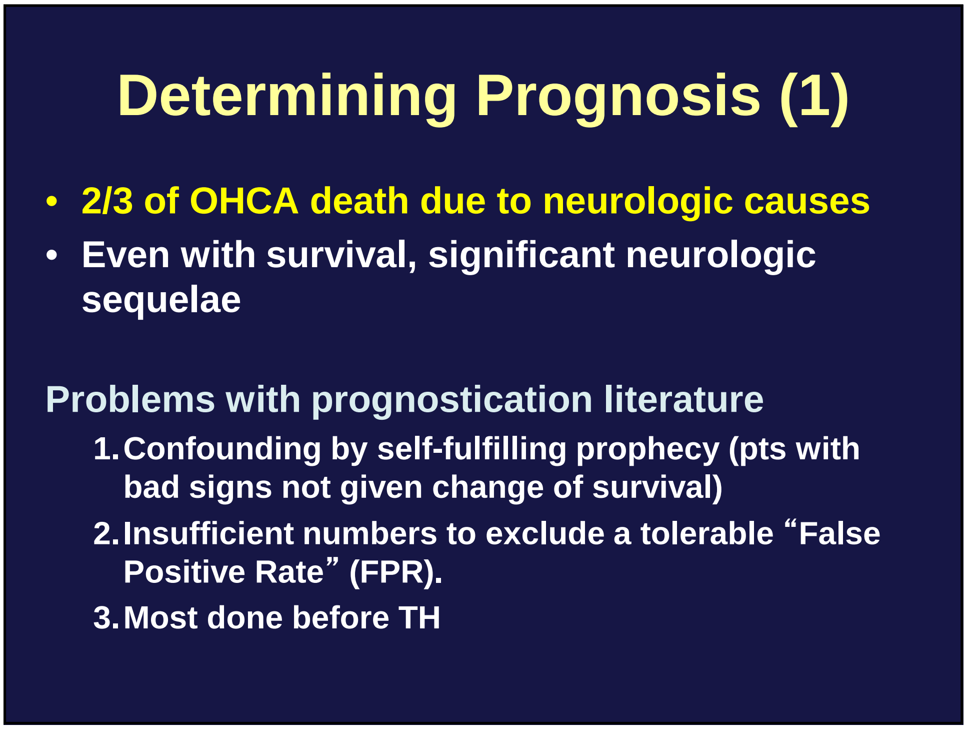
Seizures and Myoclonus

- Seizures / myoclonus occur in 5–15% of adult patients who achieve ROSC and 10-40% of those who remain comatose
- Increases cerebral metabolism 3-fold and may cause cerebral injury
- Requires urgent treatment
- Myoclonus can be particularly difficult to treat
- *Seizure activity difficult to identify with NMBA and hard to differentiate from shivering.*



Return to Normothermia

- Begin re-warming 24h post-initiation
- Re-warm rate of 0.25ºC(~0.5ºF)/h)
- Maintain paralytic/sedation until re-warmed
- When patient achieves 96.8F/36C:
  - D/C NMBA (if started) and then sedation
- After re-warming, avoid hyperthermia, which is bad for neurologic recovery.
- Once returned to 98.6F, can begin to assess for neurologic recovery and prognosis

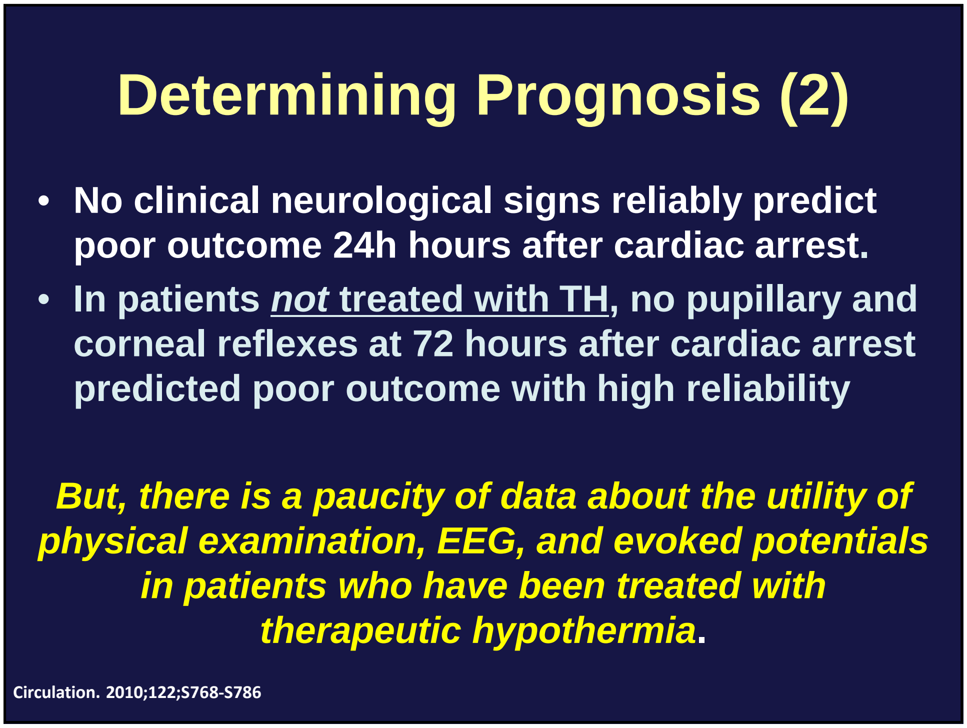


Determining Prognosis (1)

- 2/3 of OHCA death due to neurologic causes
- Even with survival, significant neurologic sequelae

Problems with prognostication literature

1. Confounding by self-fulfilling prophecy (pts with bad signs not given change of survival)
2. Insufficient numbers to exclude a tolerable “False Positive Rate” (FPR).
3. Most done before TH



Determining Prognosis (2)

- No clinical neurological signs reliably predict poor outcome 24h hours after cardiac arrest.
- In patients *not* treated with TH, no pupillary and corneal reflexes at 72 hours after cardiac arrest predicted poor outcome with high reliability

But, there is a paucity of data about the utility of physical examination, EEG, and evoked potentials in patients who have been treated with therapeutic hypothermia.

Circulation. 2010;122;S768-S786

Prognosis - Recommendations

- *The earliest time for prognostication using clinical examination in patients treated with TTM, where sedation or paralysis could be a confounder, may be 72 hours after return to normothermia.*
- *Operationally, the timing for prognostication is typically 4.5 to 5 days after ROSC for patients treated with TTM.* *AHA Guidelines 2015*

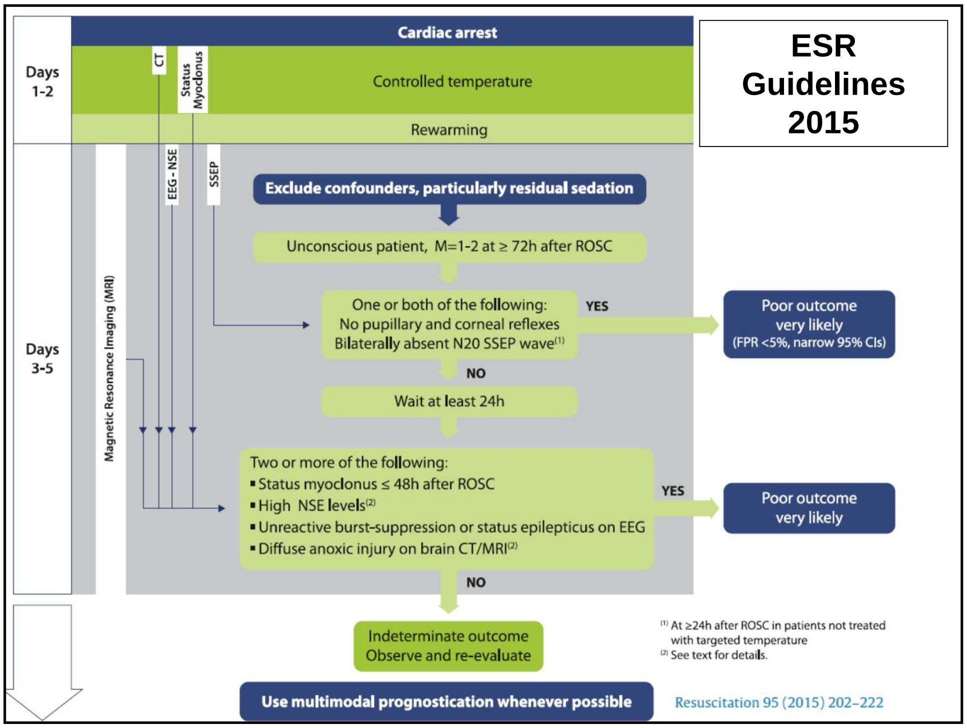
Wait for > 72 hours of normothermia, and in many cases, even longer

---

TTM Prognostic Criteria

Only discontinue active intensive care if:

- Brain death due to cerebral herniation.
- Severe myoclonus status in the first 24 hours after admission and a bilateral absence of N20-peak on SSEP.
- >72 hours after normothermia: persisting coma with a Glasgow Motor Score 1-2 and bilateral absence of N20-peak on SSEP.
- >72 hours after normothermia: persisting coma with a Glasgow Motor Score 1-2 and a treatment refractory status epilepticus.



ESR Guidelines 2015

Days 1-2
Days 3-5
Cardiac arrest
CT
Status Myoclonus
Controlled temperature
Rewarming
EEG - NSE
SSEP
Magnetic Resonance Imaging (MRI)

Exclude confounders, particularly residual sedation

Unconscious patient, M=1-2 at ≥ 72h after ROSC

One or both of the following:
No pupillary and corneal reflexes
Bilaterally absent N20 SSEP wave[(1)]

YES → Poor outcome very likely (FPR <5%, narrow 95% CIs)

NO

Wait at least 24h

Two or more of the following:
- Status myoclonus ≤ 48h after ROSC
- High NSE levels[(2)]
- Unreactive burst-suppression or status epilepticus on EEG
- Diffuse anoxic injury on brain CT/MRI[(2)]

YES → Poor outcome very likely

NO

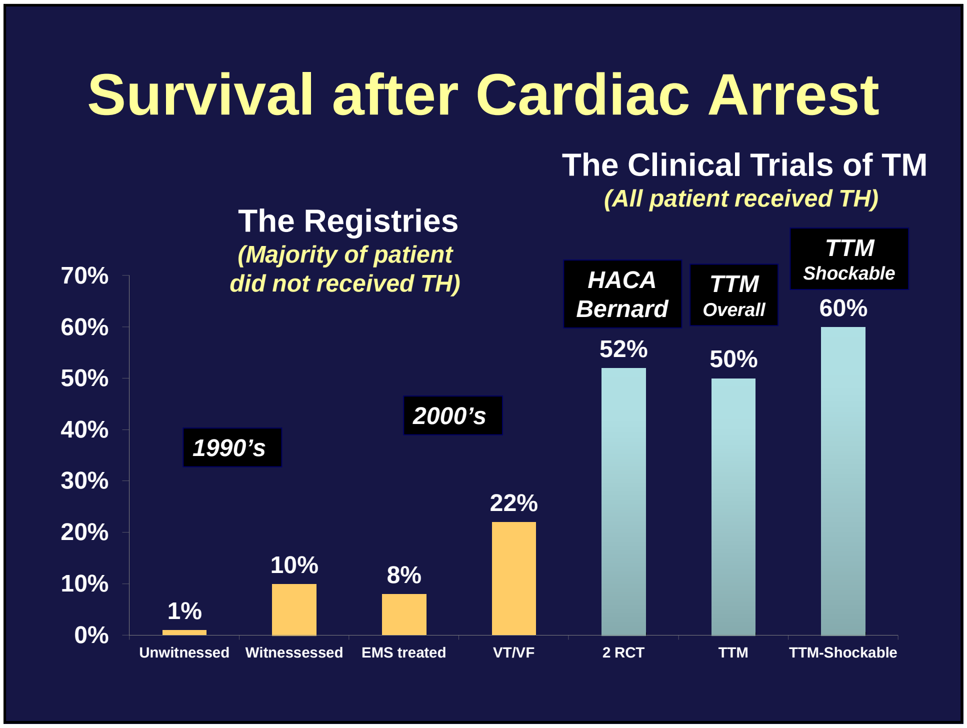
Indeterminate outcome
Observe and re-evaluate

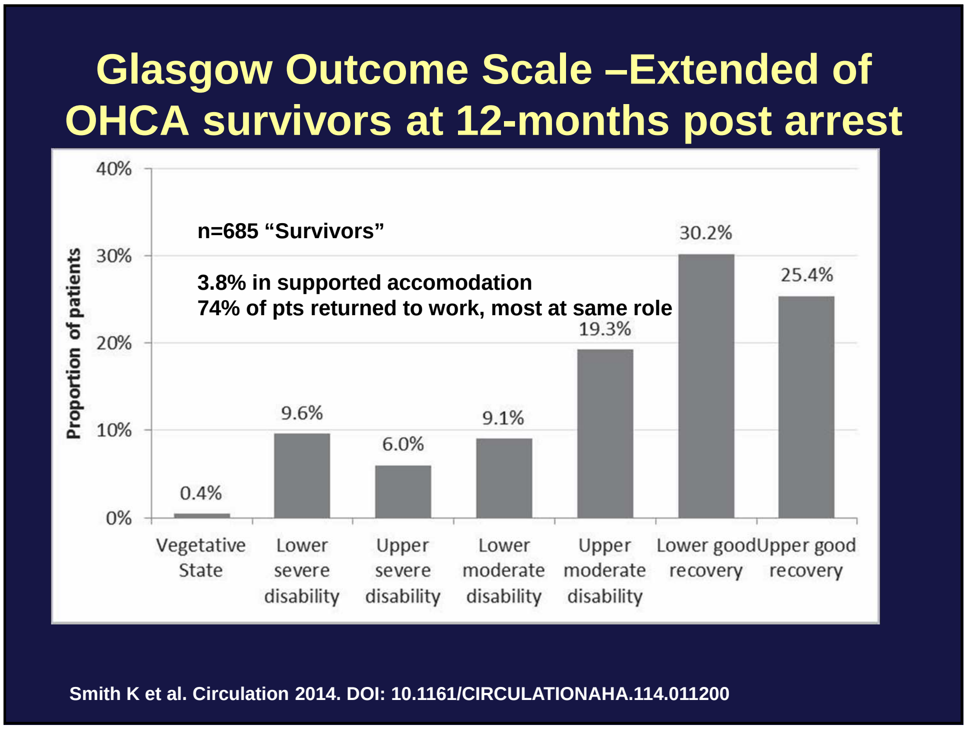
Use multimodal prognostication whenever possible

[(1)] At ≥24h after ROSC in patients not treated with targeted temperature
[(2)] See text for details.

Resuscitation 95 (2015) 202–222

Survival after Cardiac Arrest



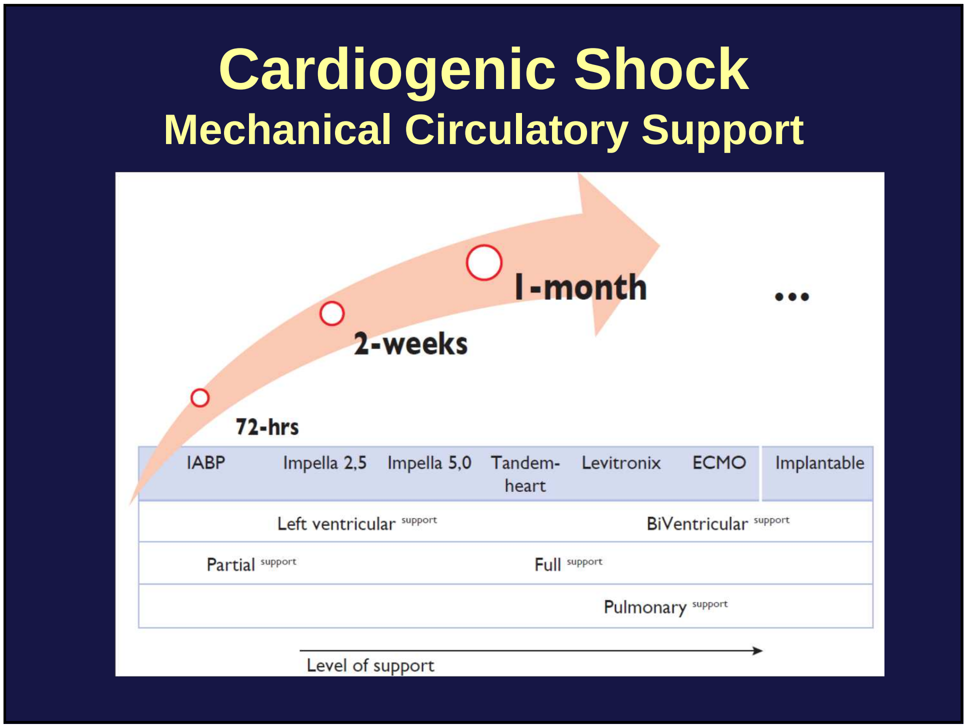


Glasgow Outcome Scale –Extended of OHCA survivors at 12-months post arrest

n=685 “Survivors”

3.8% in supported accomodation
74% of pts returned to work, most at same role

Smith K et al. Circulation 2014. DOI: 10.1161/CIRCULATIONAHA.114.011200



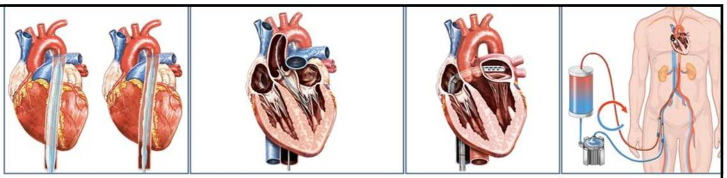
Cardiogenic Shock

Mechanical Circulatory Support

72-hrs
2-weeks
1-month
...
IABP
Impella 2,5
Impella 5,0
Tandem-heart
Levitronix
ECMO
Implantable
Left ventricular support
BiVentricular support
Partial support
Full support
Pulmonary support
Level of support

Percutaneous Ventricular Assist Devices

(J Am Coll Cardiol Intv 2016;9:871-83)



	IABP	IMPELLA	TANDEMHEART	VA-ECMO
Cardiac Flow	0.3-0.5 L/ min	1-5L/ min (Impella 2.5, Impella CP, Impella 5)	2.5-5 L/ min	3-7 L-min
Mechanism	Aorta	LV → AO	LA → AO	RA → AO
Maximum implant days	Weeks	7 days	14 days	Weeks
Sheath size	7-8 Fr	13-14 Fr Impella 5.0 - 21 Fr	15-17 Fr Arterial 21 Fr Venous	14-16 Fr Arterial 18-21 Fr Venous
Femoral Artery Size	>4 mm	Impella 2.5 & CP - 5-5.5 mm Impella 5 - 8 mm	8 mm	8 mm
Cardiac synchrony or stable rhythm	Yes	No	No	No
Afterload	↓	↓	↑	↑↑↑
MAP	↑	↑↑	↑↑	↑↑
Cardiac Flow	↑	↑↑	↑↑	↑↑
Cardiac Power	↑	↑↑	↑↑	↑↑
LVEDP	↓	↓↓	↓↓	↔
PCWP	↓	↓↓	↓↓	↔
LV Preload	---	↓↓	↓↓	↓
Coronary Perfusion	↑	↑	---	---
Myocardial oxygen demand	↓	↓↓	↔↓	↔

Conclusion

- Establish post-cardiac arrest care algorithm
- Therapeutic hypothermia has a Class I indication for OHCA from VT/VF arrest
- Evidence for TH less strong in non-VT/VF arrest, but is a reasonable option (and Class I indication
- Establishment of detailed protocol for TH critical for successful implementation
- Review cases of TH, establish metrics, and constantly educate

References

- Nolan JP et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 95 (2015) 202–222
- Rossetti AO et al. Neurological prognostication of outcome in patients in coma after cardiac arrest. Lancet Neurol 2016; 15: 597–609
- Part 8: Post–Cardiac Arrest Care -2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132[suppl 1]:S465–S482.
- Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549-556
- Bernard SA, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557-563
- Scirica BM. Therapeutic hypothermia after cardiac arrest. *Circulation*. 2013;127:244-25
- Nielsen N, et al. Targeted temperature management at 33° C versus 36° C after cardiac arrest.N Engl J Med. 2013 Dec 5;369(23):2197-206

QUESTION 1:

In a patients with an unwitnessed VF cardiac arrest and STEMI, what is the most appropriate sequence of events?

A. ACLS, primary PCI, head CT, initiate cooling

B. ACLS, IV amiodarone, initiate cooling, primary PCI

C. ACLS, initiate cooling, primary PCI

D. ACLS, head CT, initiate cooling, primary PCI

ANSWER TO QUESTION 1:
In a patients with an unwitnessed VF cardiac arrest and STEMI, what is the most appropriate sequence of events?

A. ACLS, primary PCI, head CT, initiate cooling

B. ACLS, IV amiodarone, initiate cooling, primary PCI

C. ACLS, initiate cooling, primary PCI

D. ACLS, head CT, initiate cooling, primary PCI

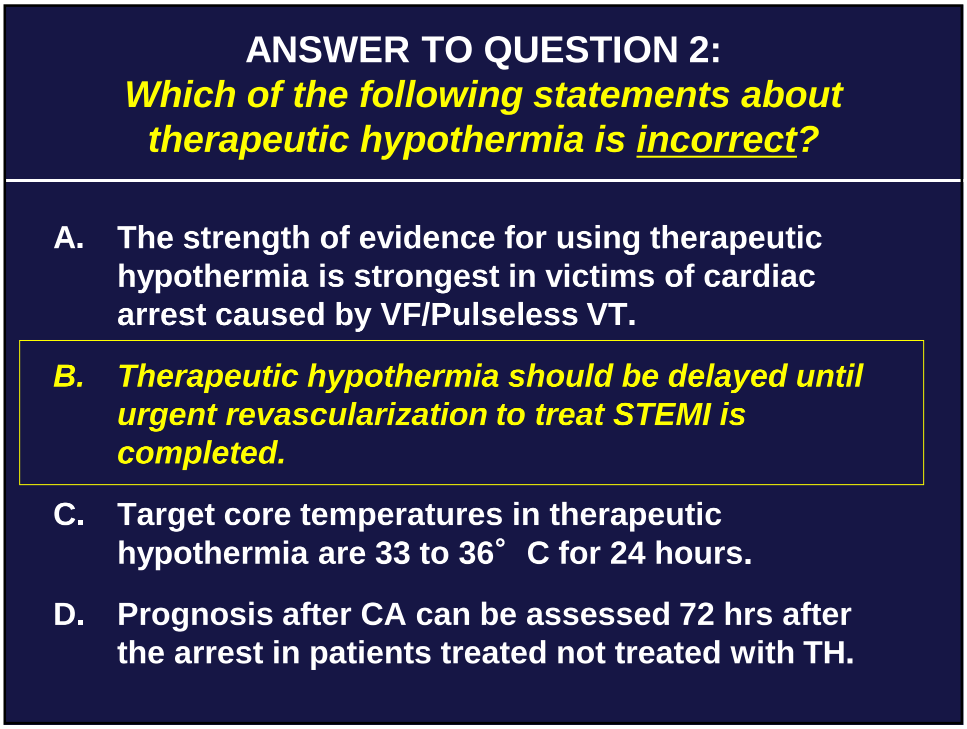
QUESTION 2:
Which of the following statements about therapeutic hypothermia is incorrect?

A. The strength of evidence for using therapeutic hypothermia is strongest in victims of cardiac arrest caused by VF/Pulseless VT.

B. Therapeutic hypothermia should be delayed until urgent revascularization to treat STEMI is completed.

C. Target core temperatures in therapeutic hypothermia are 32 to 34 ° C for 12-24 hours.

D. Prognosis after CA can be assessed 72 hrs after the arrest in patients treated with TH.



ANSWER TO QUESTION 2:

Which of the following statements about therapeutic hypothermia is incorrect?

A. The strength of evidence for using therapeutic hypothermia is strongest in victims of cardiac arrest caused by VF/Pulseless VT.

B. Therapeutic hypothermia should be delayed until urgent revascularization to treat STEMI is completed.

C. Target core temperatures in therapeutic hypothermia are 33 to 36° C for 24 hours.

D. Prognosis after CA can be assessed 72 hrs after the arrest in patients treated not treated with TH.

PULMONARY EMBOLISM IN THE ICU

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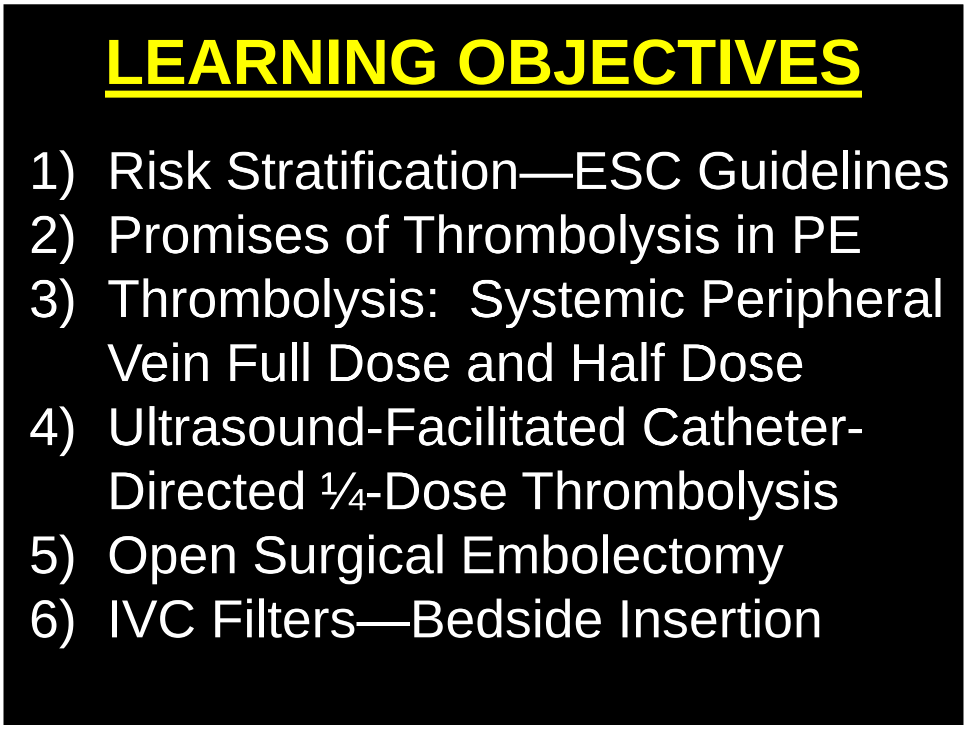
DISCLOSURES

Research Support:

BI, BMS, Daiichi, BTG EKOS, Janssen, Portola, Bio2

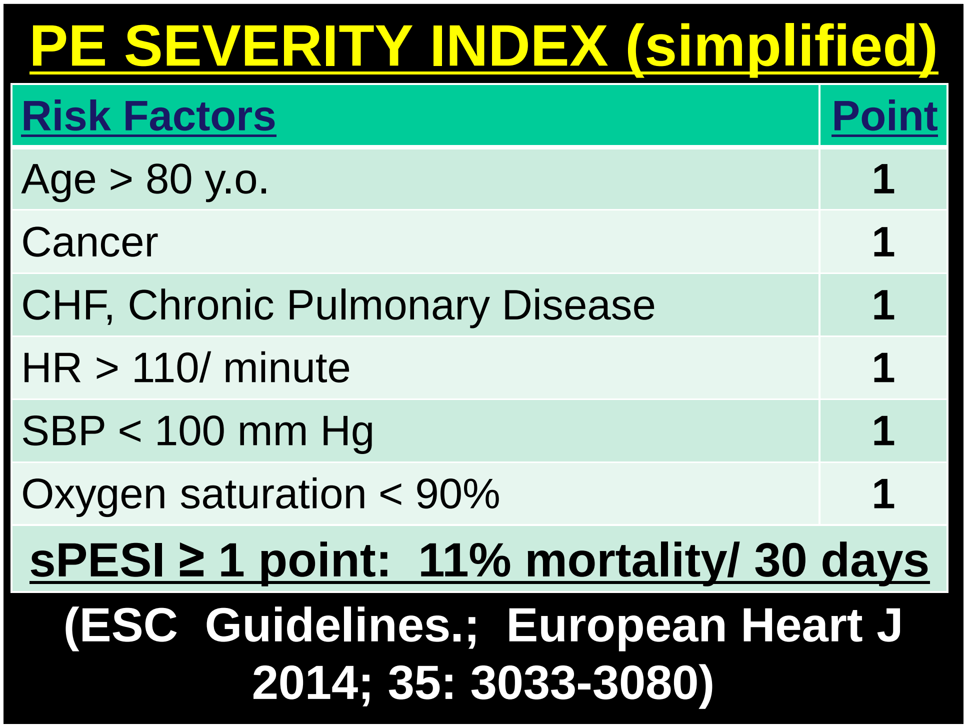
Consultant:

BI, Bayer, Daiichi, Janssen, Zafgen



LEARNING OBJECTIVES

1) Risk Stratification—ESC Guidelines
2) Promises of Thrombolysis in PE
3) Thrombolysis: Systemic Peripheral Vein Full Dose and Half Dose
4) Ultrasound-Facilitated Catheter-Directed ¼-Dose Thrombolysis
5) Open Surgical Embolectomy
6) IVC Filters—Bedside Insertion

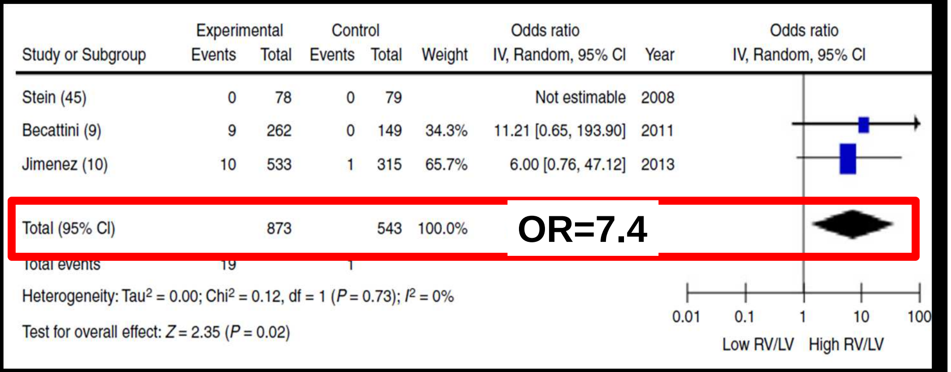


PE SEVERITY INDEX (simplified)

Risk Factors	Point
Age > 80 y.o.	**1**
Cancer	**1**
CHF, Chronic Pulmonary Disease	**1**
HR > 110/ minute	**1**
SBP < 100 mm Hg	**1**
Oxygen saturation < 90%	**1**
sPESI ≥ 1 point: 11% mortality/ 30 days	

(ESC Guidelines.; European Heart J 2014; 35: 3033-3080)

HIGH RV/LV RATIO ON CT INCREASES PE-RELATED MORTALITY



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio IV, Random, 95% CI	Year
Stein (45)	0	78	0	79		Not estimable	2008
Becattini (9)	9	262	0	149	34.3%	11.21 [0.65, 193.90]	2011
Jimenez (10)	10	533	1	315	65.7%	6.00 [0.76, 47.12]	2013
Total (95% CI)		873		543	100.0%	OR=7.4	
Total events	19		1				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.12, df = 1 (P = 0.73); I^2 = 0%

Test for overall effect: Z = 2.35 (P = 0.02)

(Trujillo-Santos J. J Thromb Haemost 2013;11: 1823)

RISK STRATIFY TO GUIDE MANAGEMENT STRATEGY

5%	10%	15%	70%
High Risk	Submassive High: RVD+Tn	Submassive Low: RVD or Tn	Low Risk
Reperfuse: Lysis/ Embolectomy	Reperfuse, Or Watch And Wait	Hospitalize, Anticoagulate	? Early Discharge; Anticoagulate

(ESC Guidelines. European Heart J 2014; 35: 3033-3080)

ADVANCED RX FOR PE

1) Systemically administered (via peripheral IV) thrombolysis:
    - Full Dose (TPA 100 mg)
    - Half Dose (TPA 50 mg)
2) Pharmacomechanical therapy with catheter-directed (ultrasound-facilitated) thrombolysis: TPA 24 mg
3) Surgical Embolectomy
4) IVC Filter

PROMISES OF FIBRINOLYSIS IN ACUTE PE

- Reduction in death by rapid reversal of RV dysfunction
- Reduction in recurrent PE: lysis in situ of pelvic and leg DVT
- More rapid restoration of baseline functional status; **improved QOL**
- Reduction in long-term pulmonary hypertension

2 MAJOR SYSTEMIC TPA TRIALS

1) **USA Trial (N=101)**

TPA improves RV function, with trend toward reduction in recurrent PE (p=0.06); no ICH

(Lancet 1993; 341:507)

2) **MAPPET-3 (N=256)**

TPA reduces need to escalate therapy (p=0.006); no ICH

(NEJM 2002; 347: 1143)

PEITHO: EFFICACY, SAFETY

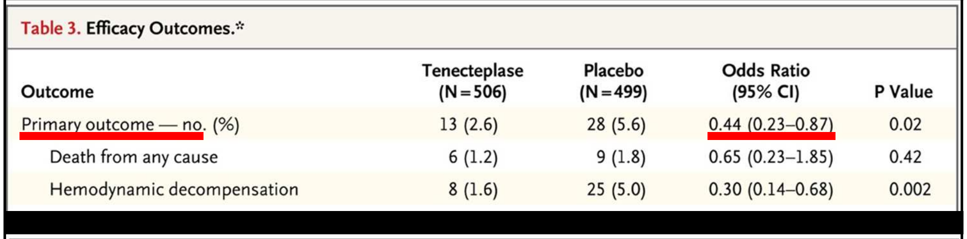


Table 3. **Efficacy Outcomes.***

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002

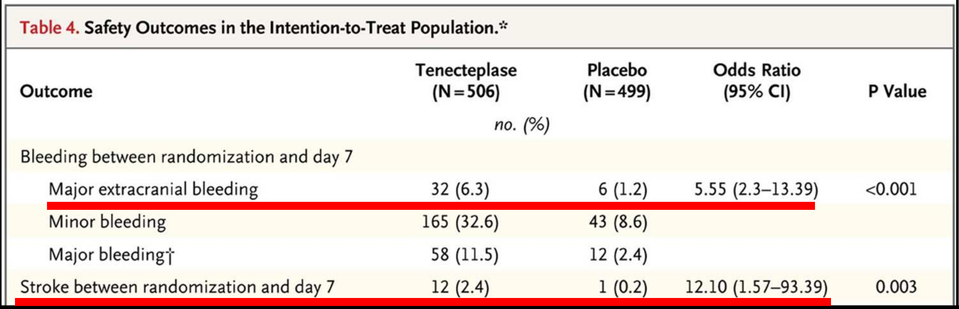
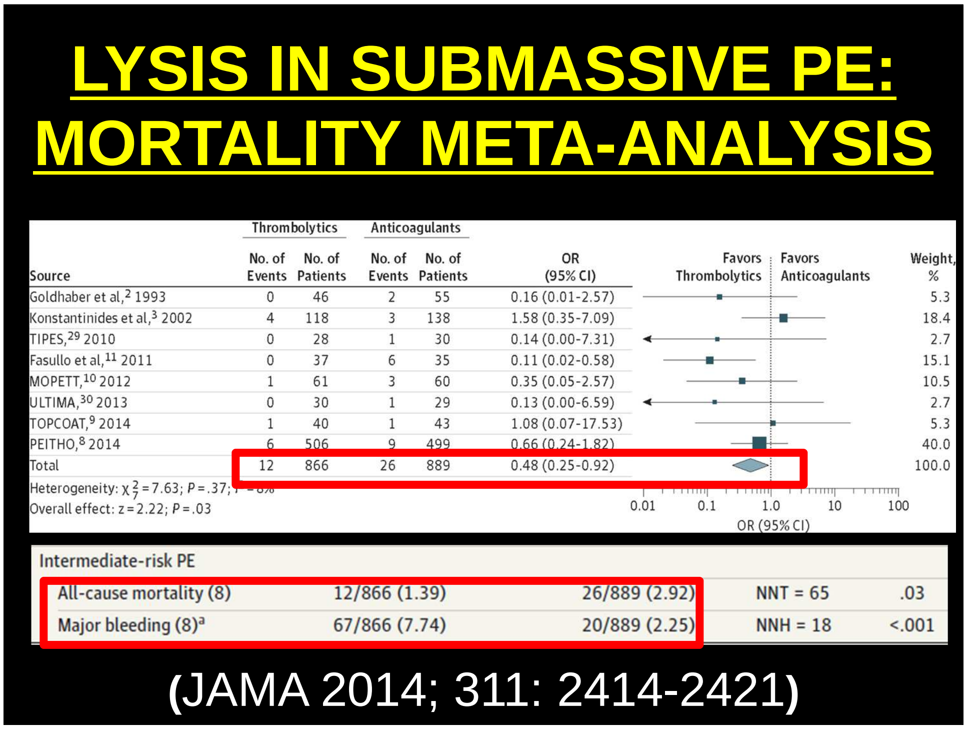


Table 4. **Safety Outcomes in the Intention-to-Treat Population.***

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003

(Meyer G et al. N Engl J Med 2014;370:1402-1411)



LYSIS IN SUBMASSIVE PE: MORTALITY META-ANALYSIS

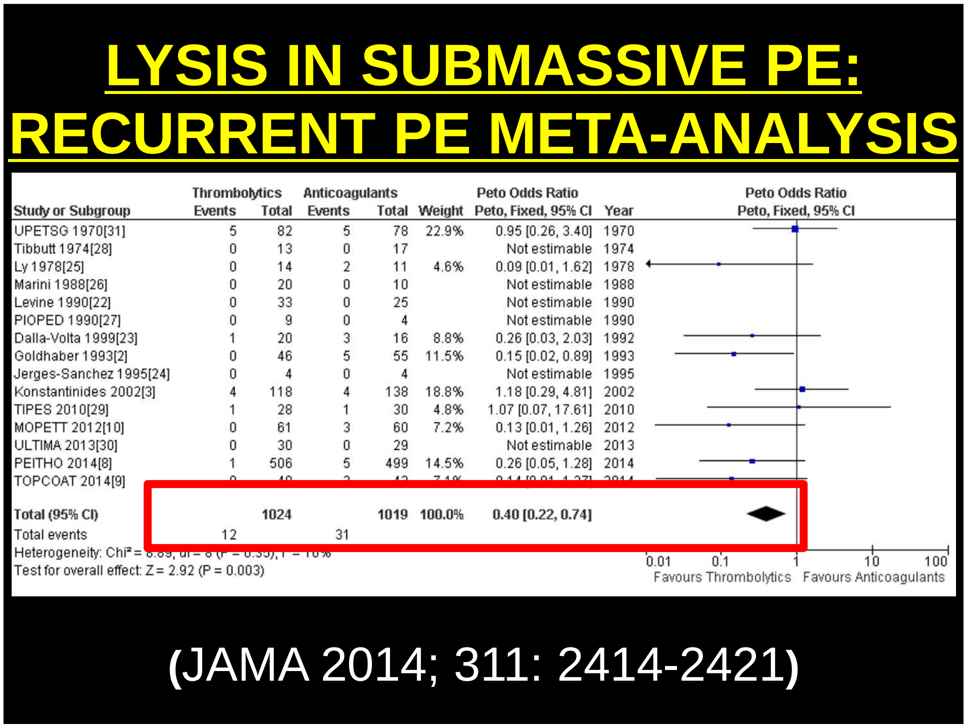
	Thrombolytics		Anticoagulants				
Source	No. of Events	No. of Patients	No. of Events	No. of Patients	OR (95% CI)	Favors Thrombolytics / Favors Anticoagulants	Weight, %
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)		5.3
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)		18.4
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)		2.7
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)		15.1
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)		10.5
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)		2.7
TOPCOAT,[9] 2014	1	40	1	43	1.08 (0.07-17.53)		5.3
PEITHO,[8] 2014	6	506	9	499	0.66 (0.24-1.82)		40.0
Total	12	866	26	889	0.48 (0.25-0.92)		100.0

Heterogeneity: $\chi^2_7 = 7.63$; $P = .37$; $I^2 = 8\%$

Overall effect: $z = 2.22$; $P = .03$

Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

(JAMA 2014; 311: 2414-2421)



LYSIS IN SUBMASSIVE PE: RECURRENT PE META-ANALYSIS

	Thrombolytics		Anticoagulants			Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Year
UPETSG 1970[31]	5	82	5	78	22.9%	0.95 [0.26, 3.40]	1970
Tibbutt 1974[28]	0	13	0	17		Not estimable	1974
Ly 1978[25]	0	14	2	11	4.6%	0.09 [0.01, 1.62]	1978
Marini 1988[26]	0	20	0	10		Not estimable	1988
Levine 1990[22]	0	33	0	25		Not estimable	1990
PIOPED 1990[27]	0	9	0	4		Not estimable	1990
Dalla-Volta 1999[23]	1	20	3	16	8.8%	0.26 [0.03, 2.03]	1992
Goldhaber 1993[2]	0	46	5	55	11.5%	0.15 [0.02, 0.89]	1993
Jerges-Sanchez 1995[24]	0	4	0	4		Not estimable	1995
Konstantinides 2002[3]	4	118	4	138	18.8%	1.18 [0.29, 4.81]	2002
TIPES 2010[29]	1	28	1	30	4.8%	1.07 [0.07, 17.61]	2010
MOPETT 2012[10]	0	61	3	60	7.2%	0.13 [0.01, 1.26]	2012
ULTIMA 2013[30]	0	30	0	29		Not estimable	2013
PEITHO 2014[8]	1	506	5	499	14.5%	0.26 [0.05, 1.28]	2014
TOPCOAT 2014[9]	0	40	2	43	7.1%	0.14 [0.01, 1.37]	2014
Total (95% CI)		**1024**		**1019**	**100.0%**	**0.40 [0.22, 0.74]**	
Total events	12		31				

Heterogeneity: $Chi^2 = 8.89$, $df = 8$ ($P = 0.35$); $I^2 = 10\%$

Test for overall effect: $Z = 2.92$ ($P = 0.003$)

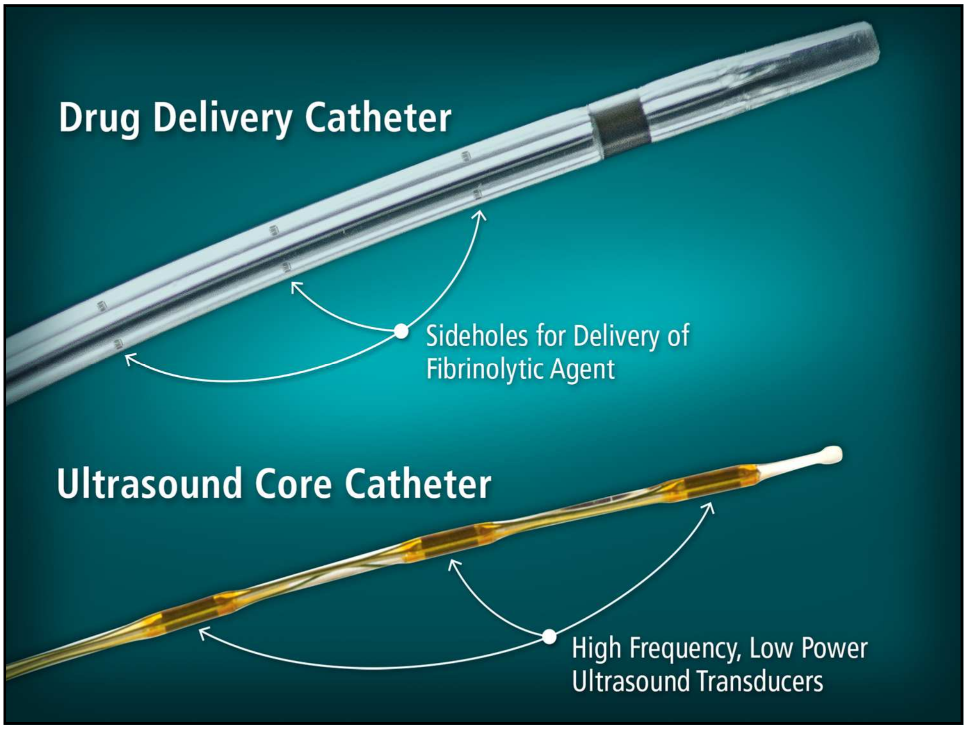
(JAMA 2014; 311: 2414-2421)

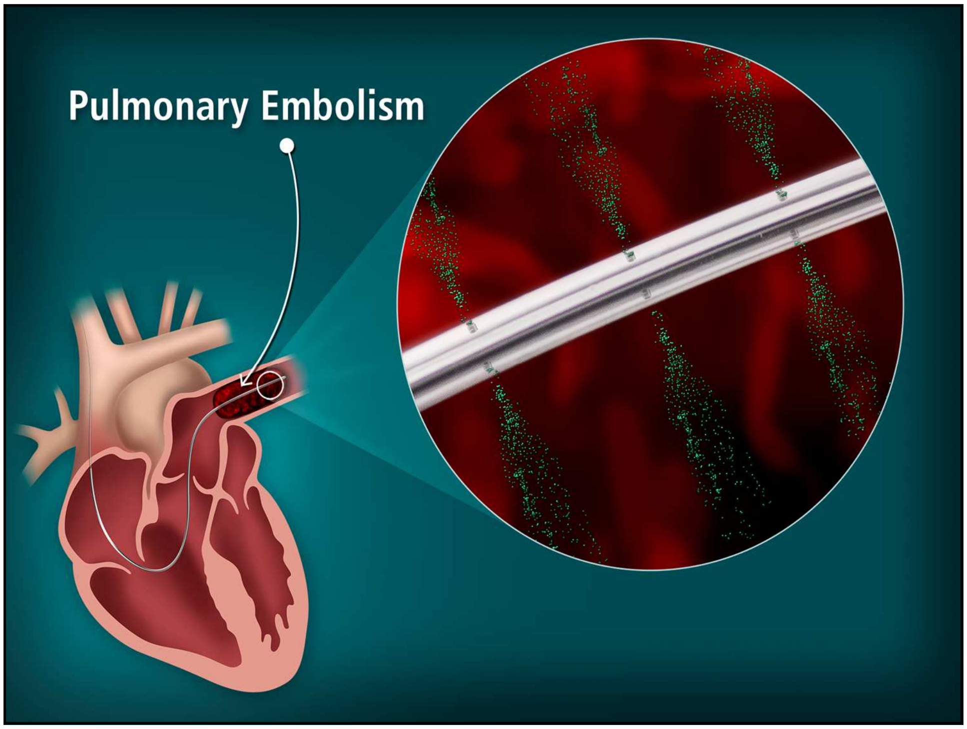
SUBMASSIVE PE: 50 mg TPA versus heparin (MOPETT) (N=121)

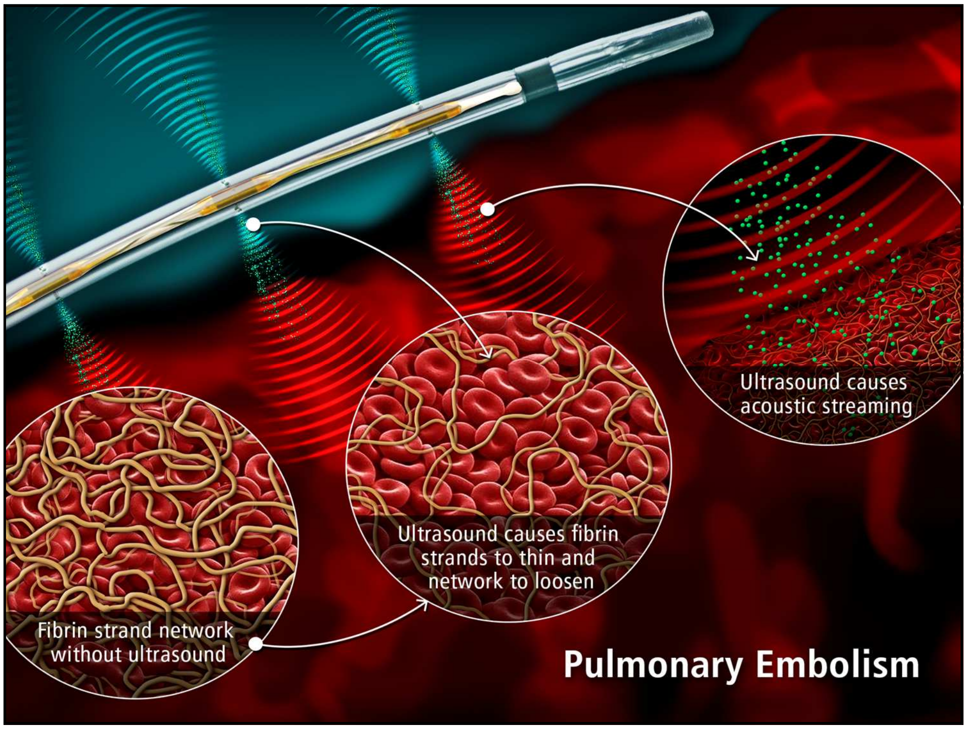
- TPA 10mg/1 min followed by 40 mg/2 h
- **No bleeding complications/ no ICH**
- PA Pressure (ECHO) lower with TPA

	TPA PA systolic	Controls	P value
Admission	**50**	**51**	**0.4**
Within 48h	**34**	**41**	**< 0.001**
6 months	**31**	**49**	**< 0.001**
28 months	**28**	**43**	**< 0.001**

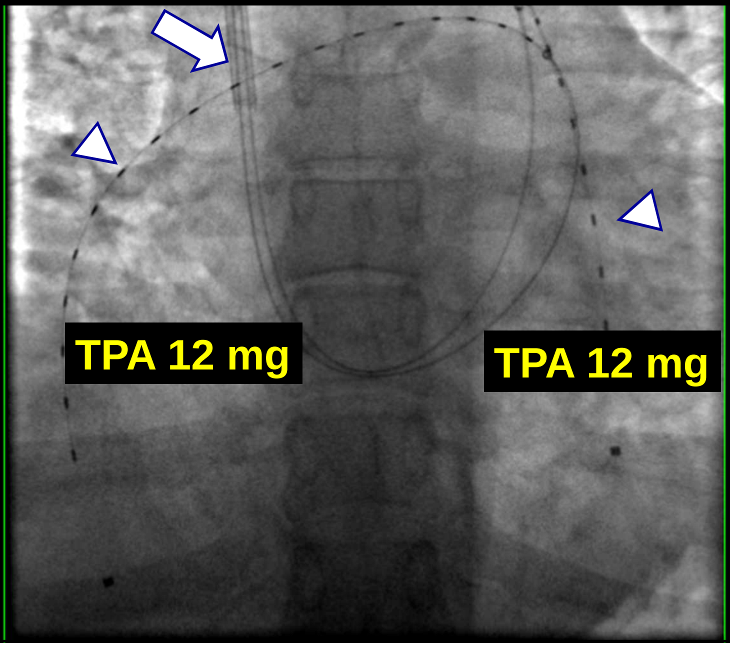
(Am J Cardiology 2013; 111: 273-277)


Drug Delivery Catheter
Sideholes for Delivery of Fibrinolytic Agent
Ultrasound Core Catheter
High Frequency, Low Power Ultrasound Transducers


Pulmonary Embolism

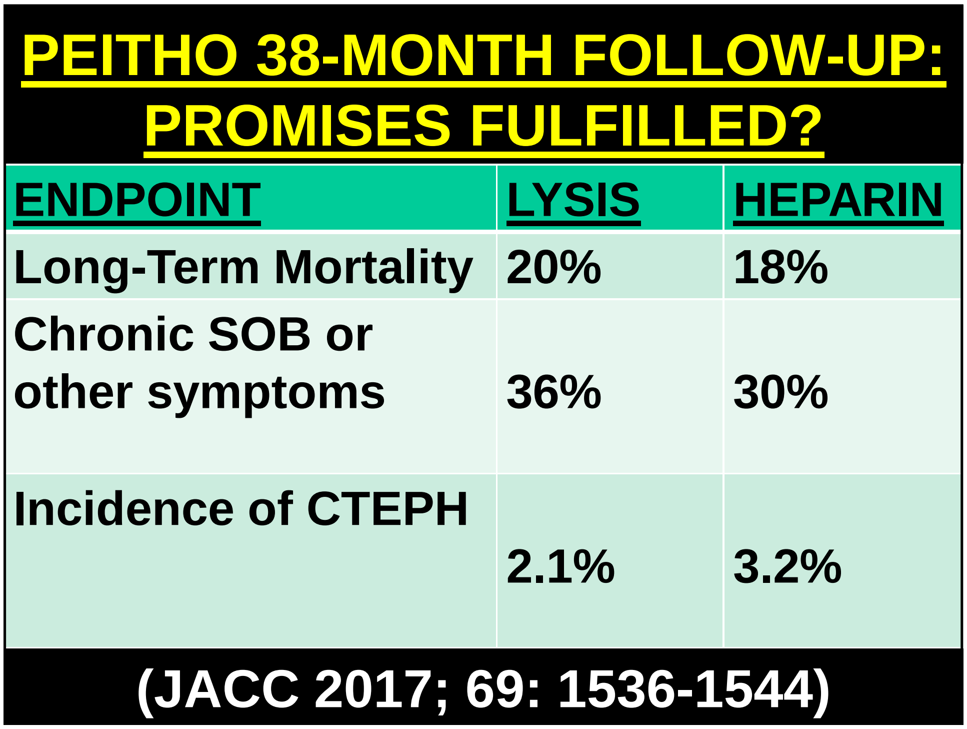

Ultrasound causes acoustic streaming
Ultrasound causes fibrin strands to thin and network to loosen
Fibrin strand network without ultrasound
Pulmonary Embolism

TPA 24 mg = total TPA dose



OVERCOMING THE HURDLE OF INTRACRANIAL HEMORRHAGE

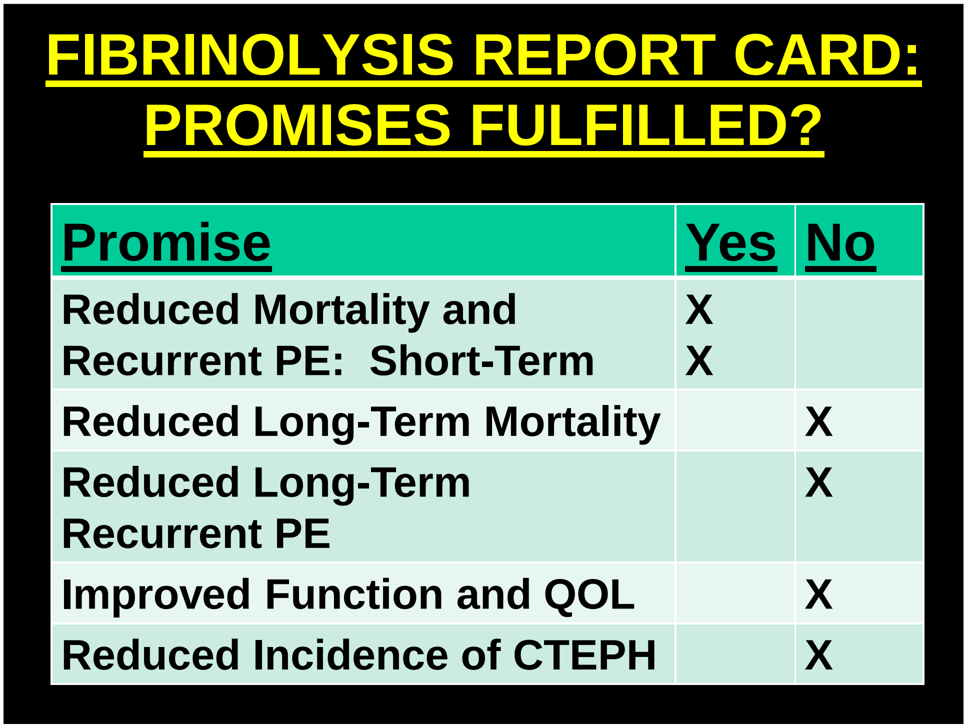
Study	ICH (Fibrinolysis)
ICOPER (Goldhaber SZ, Lancet 1999)	**9/304 (3.0%)**
PEITHO (Meyer G, NEJM 2014)	**10/506 (2.4%)**
ULTIMA (Kucher N, Circulation 2014)	**0/30 (0%)**
SEATTLE II **(Piazza G, Goldhaber SZ.** **JACC Cardiovasc Intervention;** **2015; 8: 1282-1292)**	**0/150 (0%)**



PEITHO 38-MONTH FOLLOW-UP: PROMISES FULFILLED?

ENDPOINT	LYSIS	HEPARIN
Long-Term Mortality	20%	18%
Chronic SOB or other symptoms	36%	30%
Incidence of CTEPH	2.1%	3.2%

(JACC 2017; 69: 1536-1544)

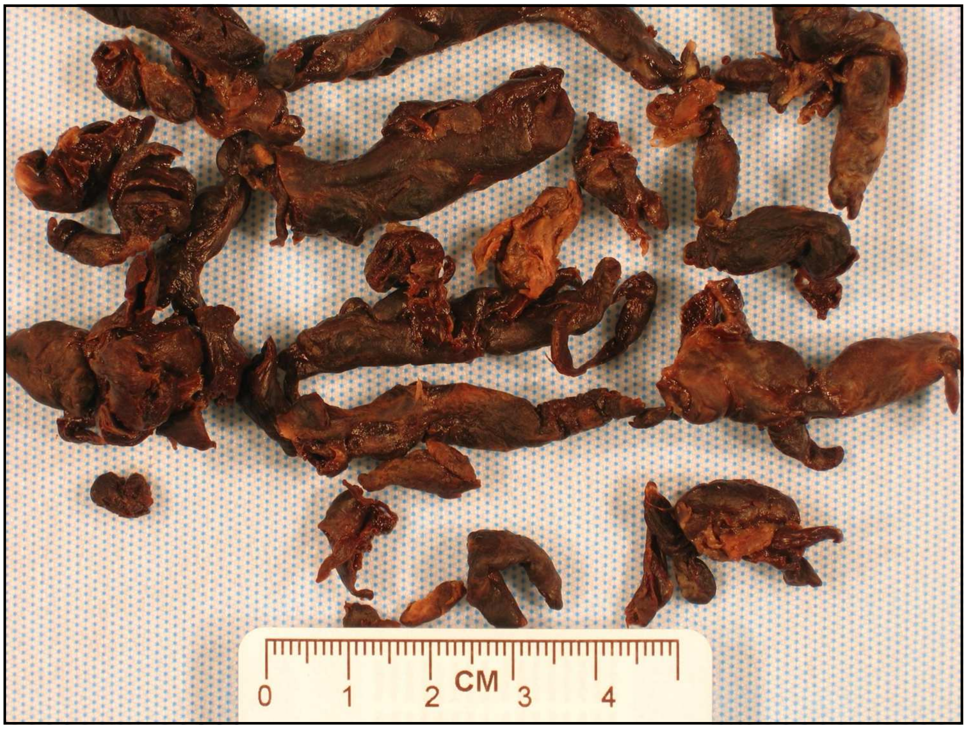


FIBRINOLYSIS REPORT CARD: PROMISES FULFILLED?

Promise	Yes	No
Reduced Mortality and Recurrent PE: Short-Term	X X	
Reduced Long-Term Mortality		X
Reduced Long-Term Recurrent PE		X
Improved Function and QOL		X
Reduced Incidence of CTEPH		X

NEW FINDINGS LEAD TO NEW QUESTIONS

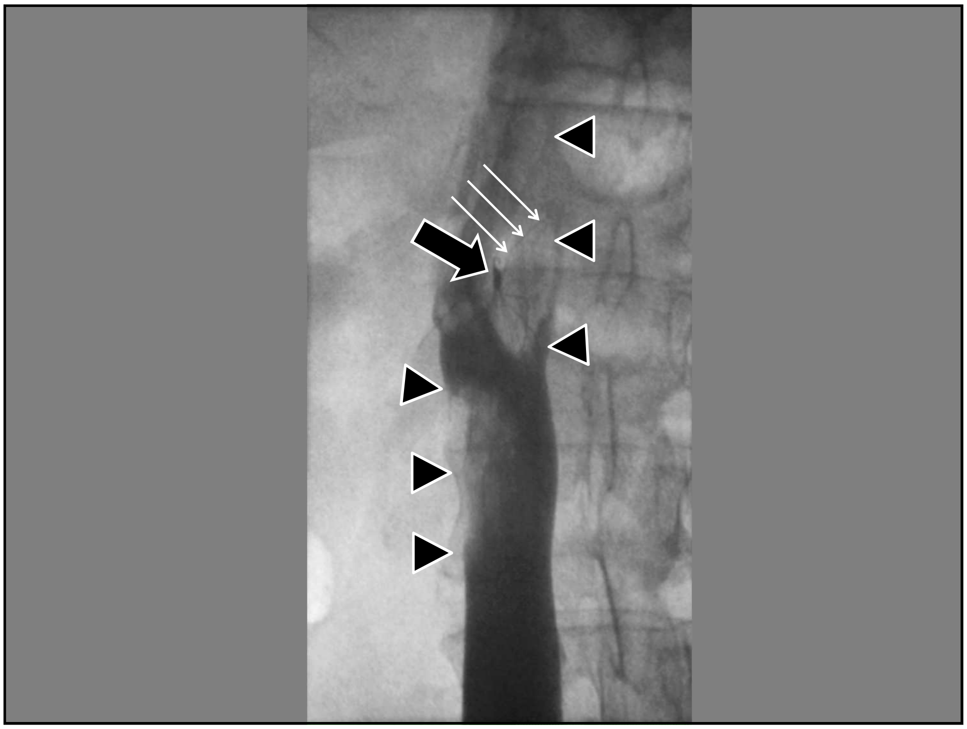
1. Have we focused too much on the large pulmonary vessels?
2. Is the explanation for lack of long-term improvement that TPA did not penetrate the microvasculature?
3. Did full-dose thrombolysis lead to micro-hemorrhage in the microvasculature?



BWH PE EMBOLECTOMIES: OPERATIVE MORTALITY (N=105)

- Overall: 6.6% (7/105)
- Massive PE: 10% (5/49)
- Submassive PE: 3.6% (2/56)

(Neely RC. Ann Thoracic Surg 2015; 100: 1245-1252)

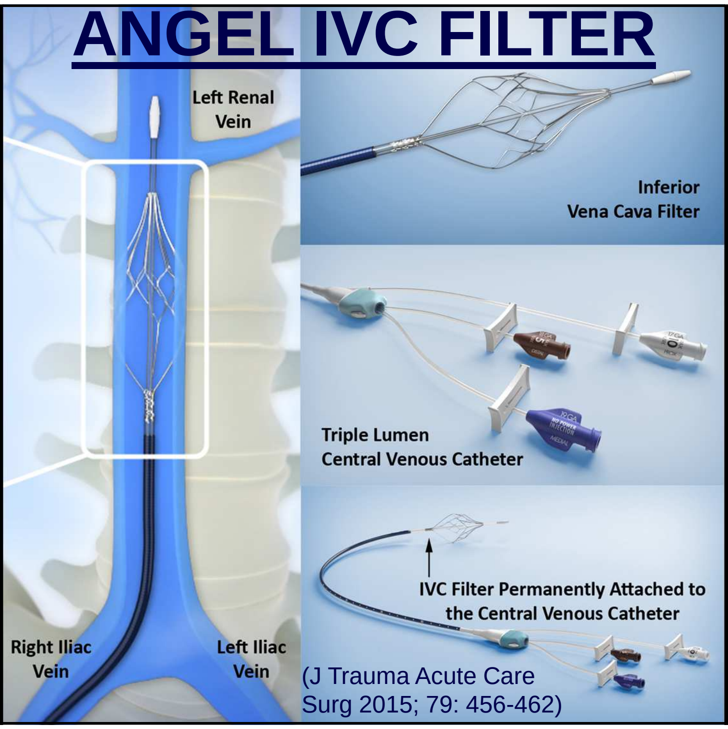


IVC FILTERS FOR PE:
AHA PE Guidelines 2011

- Contraindications to anticoagulation
- Recurrent PE despite adequate anticoagulation
- Very poor cardiopulmonary reserve, “including those with massive PE”

(Circulation 2011; 123: 1788-1830)

ANGEL IVC FILTER


Left Renal Vein
Inferior Vena Cava Filter
Triple Lumen Central Venous Catheter
IVC Filter Permanently Attached to the Central Venous Catheter
Right Iliac Vein
Left Iliac Vein

(J Trauma Acute Care Surg 2015; 79: 456-462)

TAKE HOME MESSAGES

1. Submassive PE: Fibrinolyis reduces 30-day mortality and recurrent PE but increases ICH.
2. Lower TPA doses: lower ICH rates.
3. PEITHO 3-year follow-up: no reduction in mortality, recurrent PE, symptoms, or CTEPH.
4. Angel IVC filter allows bedside insertion without fluoroscopy.

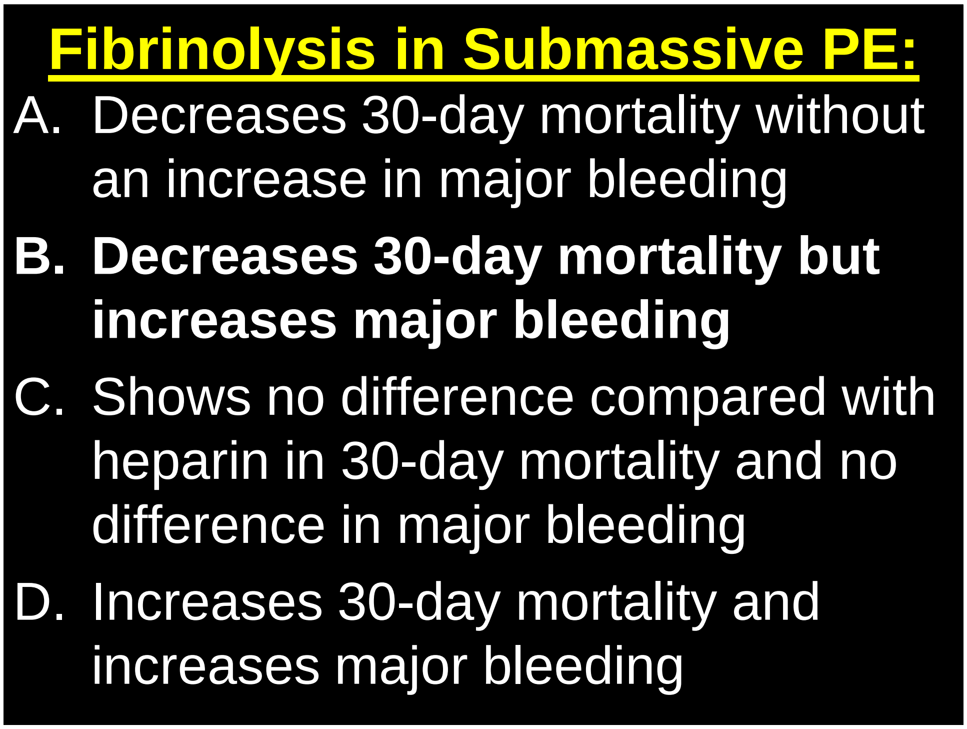
Fibrinolysis in Submassive PE:

A. Decreases 30-day mortality without an increase in major bleeding

B. Decreases 30-day mortality but increases major bleeding

C. Shows no difference compared with heparin in 30-day mortality and no difference in major bleeding

D. Increases 30-day mortality and increases major bleeding



Fibrinolysis in Submassive PE:

A. Decreases 30-day mortality without an increase in major bleeding

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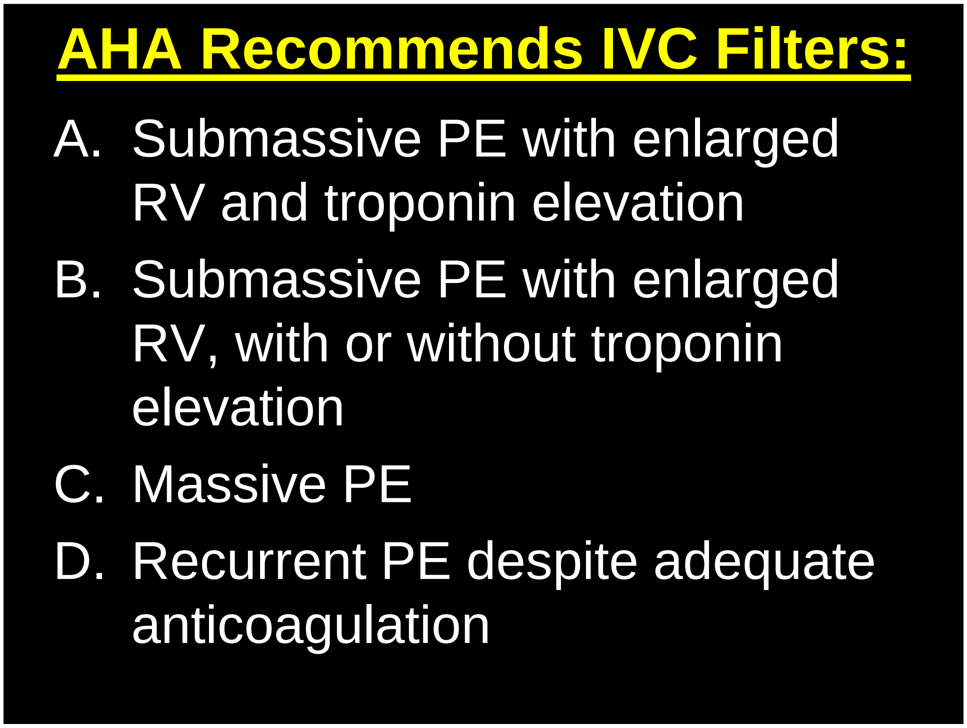

AHA Recommends IVC Filters:

A. Submassive PE with enlarged RV and troponin elevation

B. Submassive PE with enlarged RV, with or without troponin elevation

C. Massive PE

D. Recurrent PE despite adequate anticoagulation

AHA Recommends IVC Filters:

A. Submassive PE with enlarged RV and troponin elevation

B. Submassive PE with enlarged RV, with or without troponin elevation

C. Massive PE

D. Recurrent PE despite adequate anticoagulation

REFERENCES

1. PEITHO 3-year follow-up. JACC 2017; 69: 1536-1544
2. Thrombolysis in submassive PE: Meta-analysis. JAMA 2014; 311: 2414-2421
3. ESC Pulmonary Embolism Guidelines. European Heart J 2014; 35: 3033-3080

Acute Pancreatitis

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Disclosure

I have no disclosures

Outline

- Acute Pancreatitis
    - Presentation
    - Diagnosis
    - Etiology
    - Severity
    - Treatment
    - Complications

Diagnosis

- 2 of the 3 following criteria:

1) Abdominal pain consistent with the disease
2) Serum amylase and/or lipase > 3 times ULN
3) Characteristic findings on abdominal imaging

Tenner, Baillie, DeWitt. American College of Gastroenterology Guideline: Management of Acute Pancreatitis. Am J Gastro. 30 july 2013

Acute Pancreatitis- Clinical Presentation

- Epigastric, left upper quadrant pain
- Constant, with radiation to the back, chest or flanks
- Pain usually severe
- Dull, colicky, lower quadrant pain is not consistent

Tenner, Baillie, DeWitt. American College of Gastroenterology Guideline: Management of Acute Pancreatitis. Am J Gastro. 30 july 2013

Hyperlipasemia in the ICU

- Included all patients admitted to ICU with elevated lipase greater than 3 times ULN
- 159/ 417 had pancreatitis
- PPV 38.1%
- Median lipase level 1164 IU/L in patients with AP and 284.5 IU/L in patients without acute pancreatitis ($p<0.001$)
- Optimal cutoff value of lipase 532 IU/L
- Sn 77.4%, Sp78.0%, NPV 84.9%, PPV 67.0%

Cohen J. Pancreatology. 2017

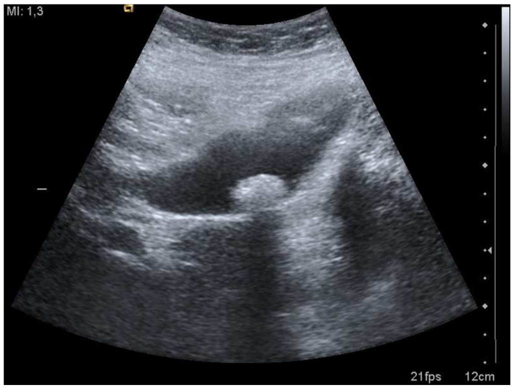
Abdominal Imaging

- CECT: 90% Sn, Sp
    - Routine use of CT unwarranted
- CT or MRI recommended if unclear dx or patient fail to improve within 48-72h, to assess local complications
    - Guideline recommendation: Strong recommendation, low quality of evidence
- MRCP may help detect CBD stones and PD disruption

Tenner. Am J Gastro. 2013
Stimac. Am J Gastro 2007

Imaging

- Abdominal ultrasound should be performed in all patients to assess gallstone pancreatitis
- Guideline recommendation: Strong recommendation, low quality of evidence



Tenner. Am J Gastro. 2013
http://upload.wikimedia.org/wikipedia/commons/8/8a/Gallstone_0414092027109.jpg

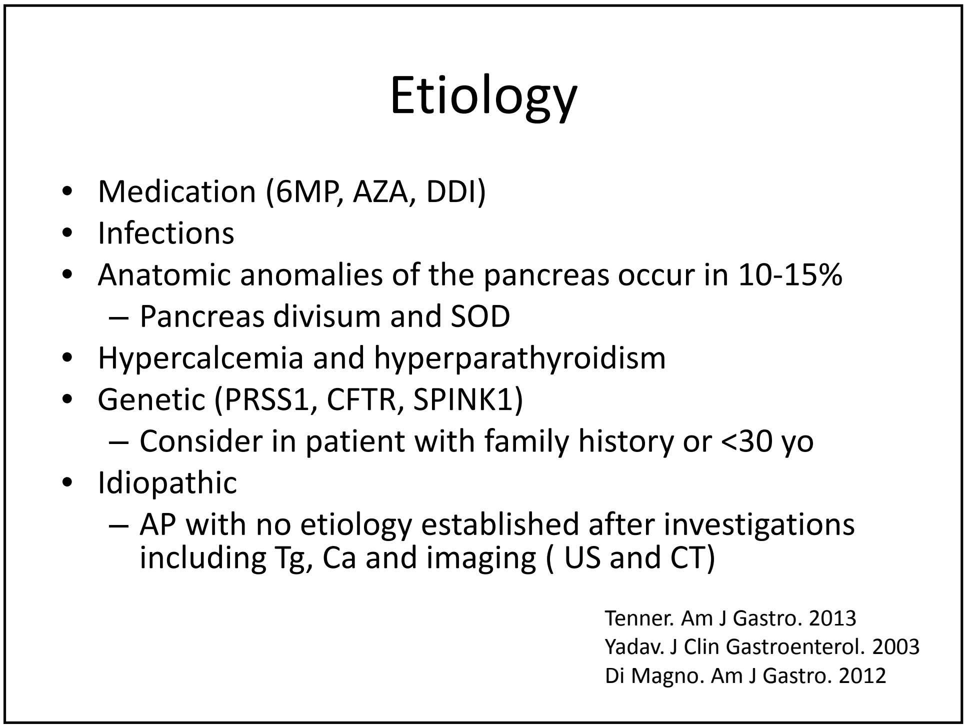
Etiology

Common	Uncommon/Rare
Gallstone Alcohol Hypertriglyceridemia ERCP Trauma Drugs (AZA, 6-MP, sulfonamide, estrogen, tetracycline, valproic acid, HAART) Sphincter of Oddi Dysfunction	Vascular/vasculitis CTD, PPT Cancer Hypercalcemia Pancreas Divisum Hereditary pancreatitis Infections (mumps, coxsackievirus, CMV, echovirus, parasites) Autoimmune (Sjogren, AIP)

Etiology

- Gallstone 40-70%
- Alcohol 25-35 %
- Hypertriglyceridemia 1-4%
  - In absence of gallstone or alcohol history Tg should be obtained, Dx considered with levels above 1000
- Main Pancreatic Duct Obstruction
  - 5-14% pancreaticobiliary tumors present with IAP
  - Adenocarcinoma to consider >40 years old

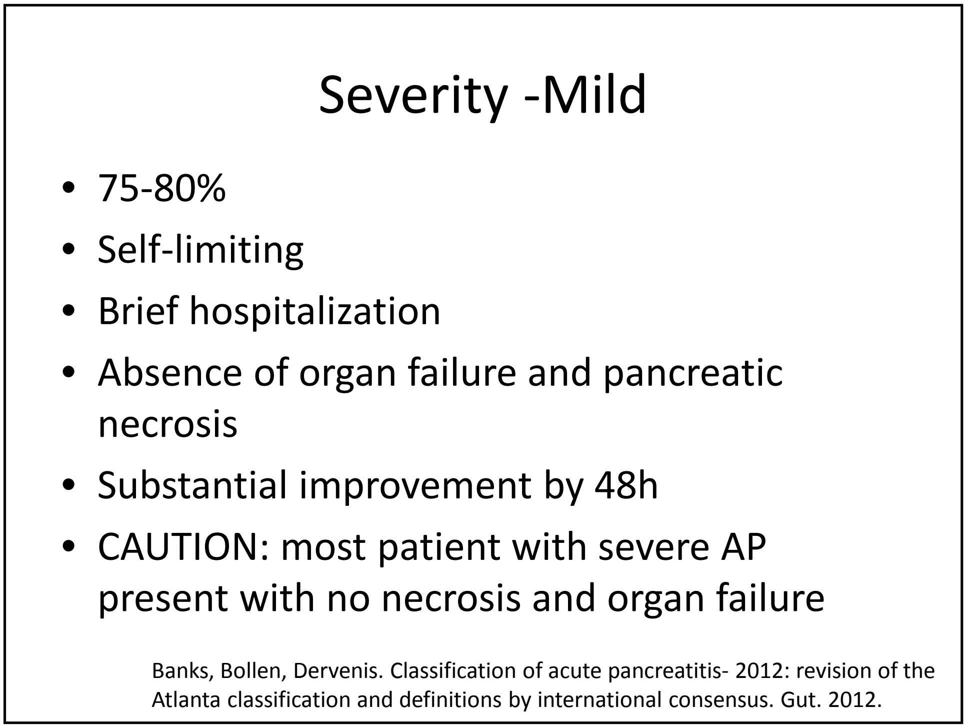
Tenner. Am J Gastro. 2013
Yadav. J Clin Gastroenterol. 2003



Etiology

- Medication (6MP, AZA, DDI)
- Infections
- Anatomic anomalies of the pancreas occur in 10-15%
  - Pancreas divisum and SOD
- Hypercalcemia and hyperparathyroidism
- Genetic (PRSS1, CFTR, SPINK1)
  - Consider in patient with family history or <30 yo
- Idiopathic
  - AP with no etiology established after investigations including Tg, Ca and imaging (US and CT)

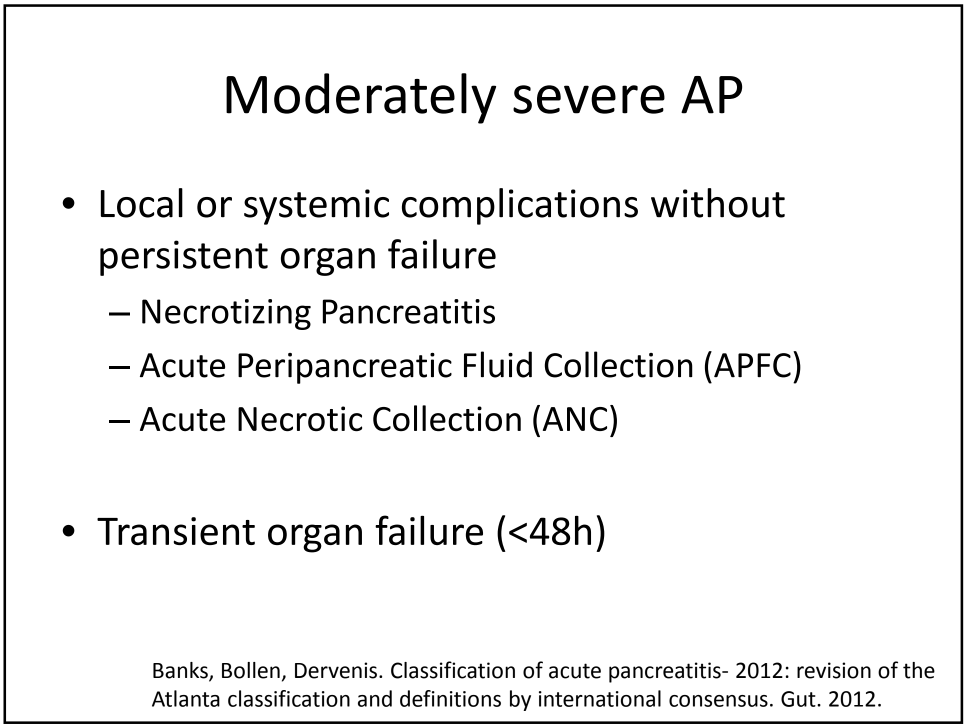
Tenner. Am J Gastro. 2013
Yadav. J Clin Gastroenterol. 2003
Di Magno. Am J Gastro. 2012



Severity -Mild

- 75-80%
- Self-limiting
- Brief hospitalization
- Absence of organ failure and pancreatic necrosis
- Substantial improvement by 48h
- CAUTION: most patient with severe AP present with no necrosis and organ failure

Banks, Bollen, Dervenis. Classification of acute pancreatitis- 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2012.

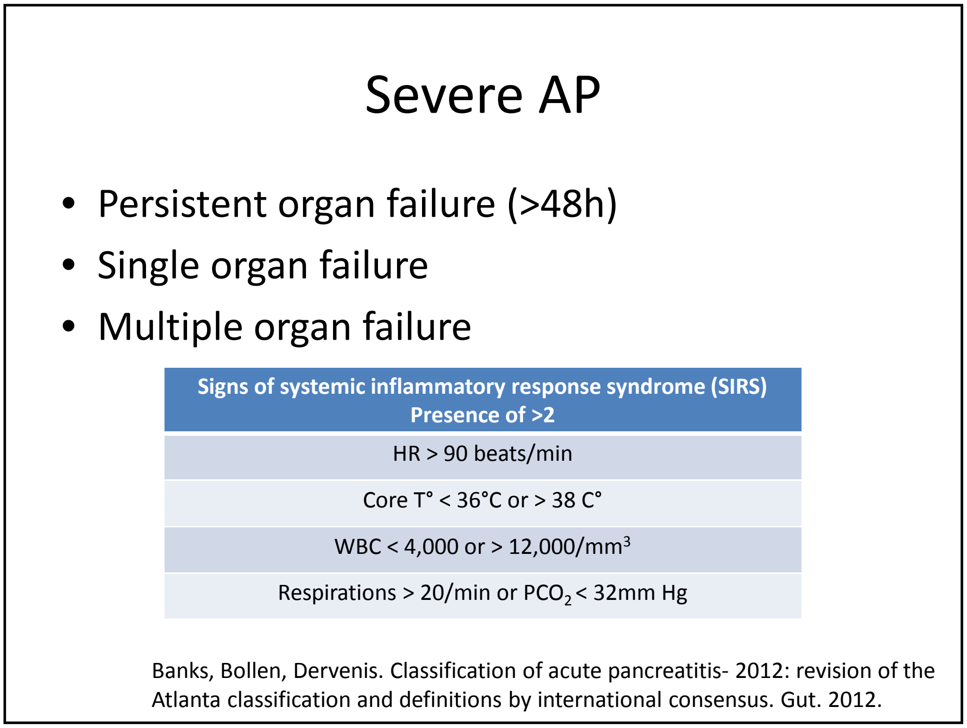


Moderately severe AP

- Local or systemic complications without persistent organ failure
  - Necrotizing Pancreatitis
  - Acute Peripancreatic Fluid Collection (APFC)
  - Acute Necrotic Collection (ANC)

- Transient organ failure (<48h)

Banks, Bollen, Dervenis. Classification of acute pancreatitis- 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2012.



Severe AP

- Persistent organ failure (>48h)
- Single organ failure
- Multiple organ failure

Signs of systemic inflammatory response syndrome (SIRS) Presence of >2
HR > 90 beats/min
Core T° < 36°C or > 38 C°
WBC < 4,000 or > 12,000/mm^3
Respirations > 20/min or PCO$_2$ < 32mm Hg

Banks, Bollen, Dervenis. Classification of acute pancreatitis- 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2012.

Risk Stratification

- Serial bedside evaluation
  - Vitals, orthostatics
  - Volume overload, ARDS
- RANSON > 3
- APACHE II > 8
- HAPS
- CRP : 48- 72h to become accurate
  - CRP > 150
- CT and MRI do not reliably determine severity as necrosis is not apparent for 24-48h

Lankisch. Clin Gastro Hep. 2009
Tenner. Am J Gastro. 2013

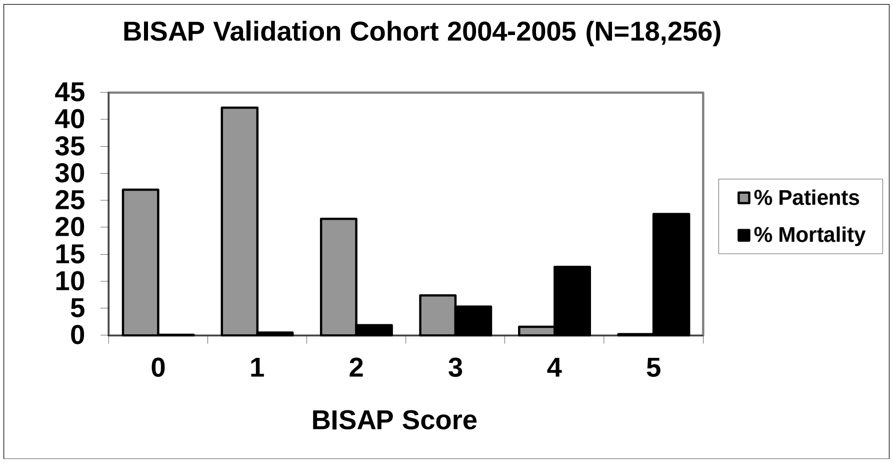
Risk Stratification
Bedside Index of Severity in Acute Pancreatitis (BISAP)

- BUN >25 mg/dL (8.9 mmol/L)
- Abnormal mental status with a Glasgow Coma Score <15
- Evidence of SIRS (systemic inflammatory response syndrome)
- Patient age >60 years old
- Imaging study reveals pleural effusion

- BISAP>2
  - Mortality 3, 4, 5 = 4, 8 and 10%

Wu. Gut. 2008
Tenner. Am J Gastro. 2013

BISAP


BISAP Validation Cohort 2004-2005 (N=18,256)

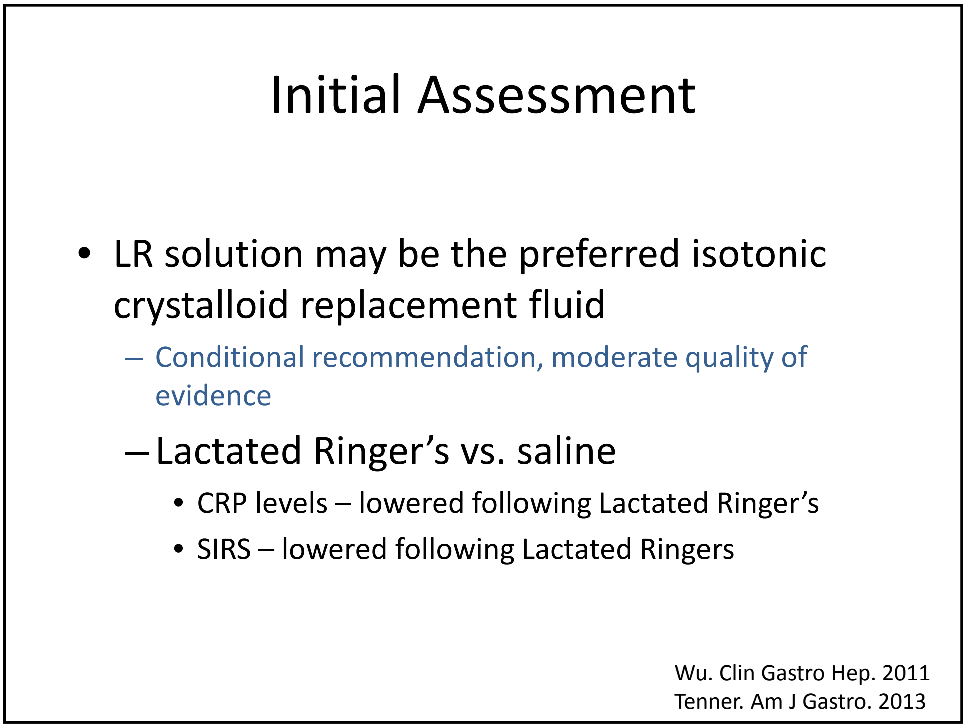
P<0.0001 test for trend

Wu et al. Gut 2008; 57: 1698-1703

Initial Assessment

- So far no medication has been shown effective in treating AP
- Aggressive hydration, defined as 250-500cc per hour (5-10cc/Kg/h) of isotonic crystalloid solution should be provided to all patients, unless CV or renal comorbidities exist
  - Strong recommendation, moderate quality of evidence
- Early aggressive IV hydration is most beneficial in the first 12-24h, and may be of little benefit beyond
  - Conditional recommendation, moderate quality of evidence

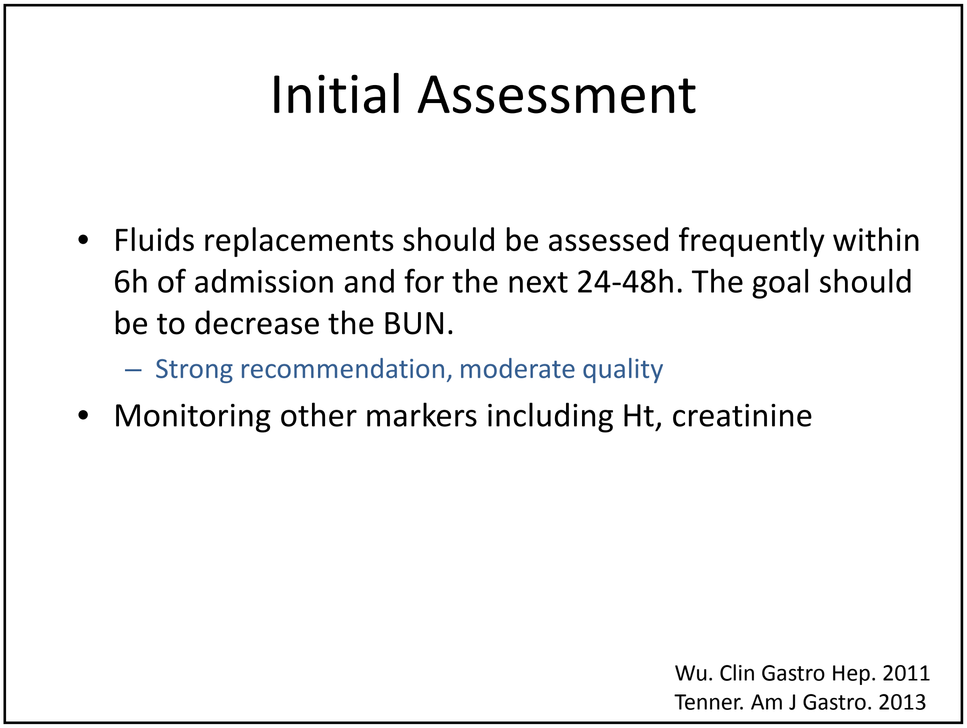
Wu. Clin Gastro Hep. 2011
Tenner. Am J Gastro. 2013



Initial Assessment

- LR solution may be the preferred isotonic crystalloid replacement fluid
  - Conditional recommendation, moderate quality of evidence
  - Lactated Ringer's vs. saline
    - CRP levels – lowered following Lactated Ringer's
    - SIRS – lowered following Lactated Ringers

Wu. Clin Gastro Hep. 2011
Tenner. Am J Gastro. 2013



Initial Assessment

- Fluids replacements should be assessed frequently within 6h of admission and for the next 24-48h. The goal should be to decrease the BUN.
  - Strong recommendation, moderate quality
- Monitoring other markers including Ht, creatinine

Wu. Clin Gastro Hep. 2011
Tenner. Am J Gastro. 2013

Initial Assessment

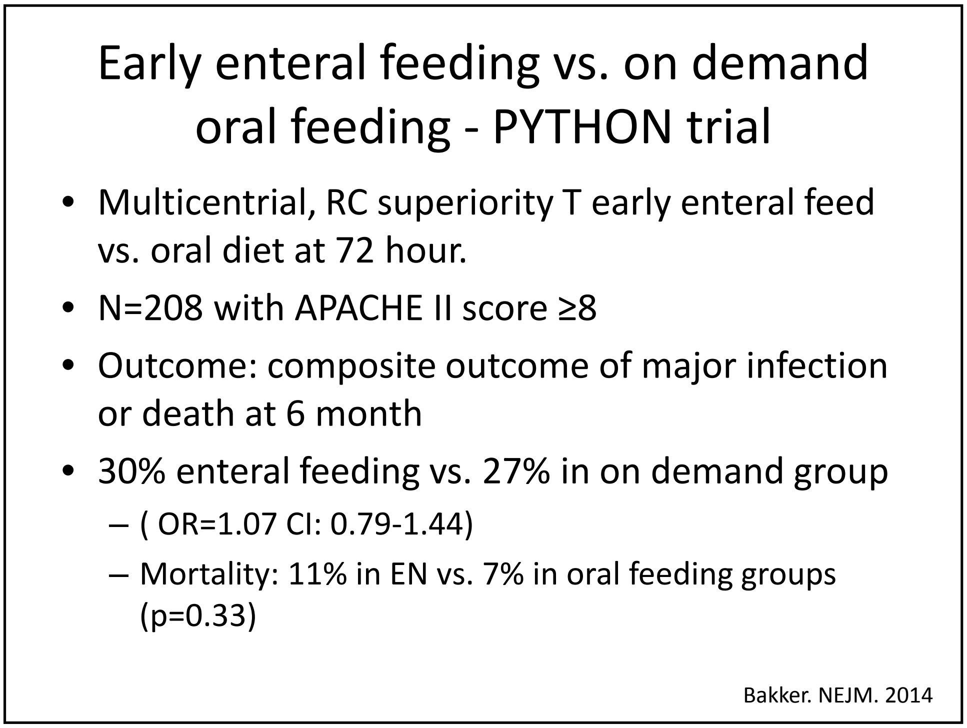
- Monitor response in urine output, orthostasis
- Maintain urine output > 0.5 cc/kg/h
- Supplemental oxygen
- Analgesia with parenteral narcotics

Wu B, Clin Gastro Hep 2011
Tenner. Am J Gastro. 2013

Nutrition

- In mild AP, oral feeding can be started immediately, if there is no nauseas and vomiting, and abdominal pain has resolved
  - Conditional recommendation, moderate quality
- In mild AP initiation of diet with low-fat diet appears as safe as clear liquid diet
  - Conditional recommendation, moderate quality
- In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided unless EN is not available, not tolerated, or not meeting the caloric requirements
  - Strong recommendation, high quality
- NG and NJ delivery of enteral feeding appear comparable in efficacy and safety
  - Strong recommendation, moderate quality

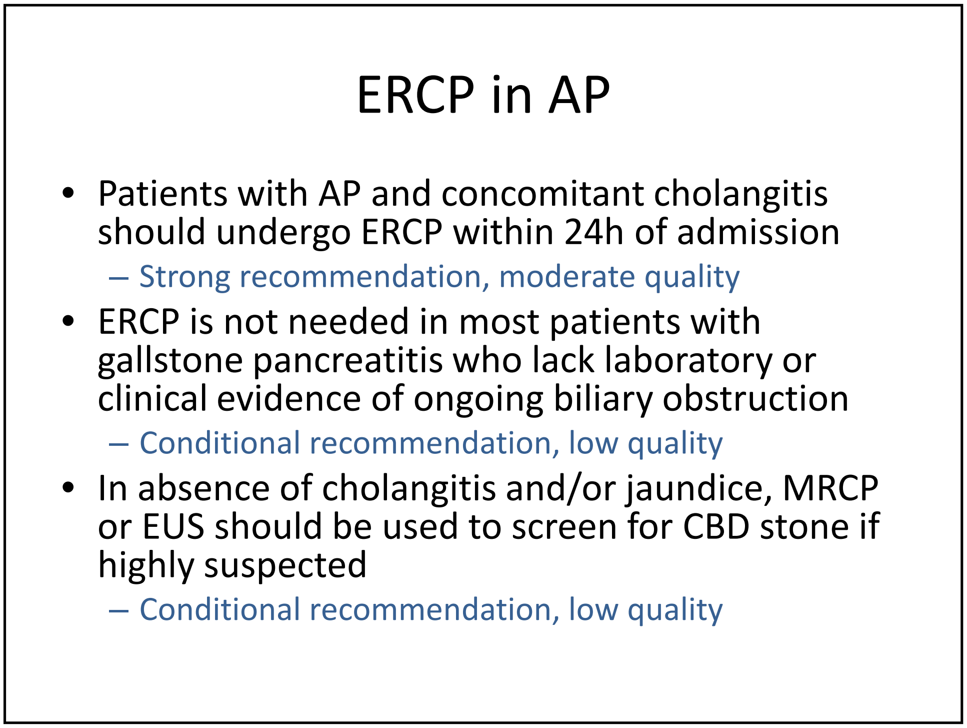
Tenner. Am J Gastro. 2013



Early enteral feeding vs. on demand oral feeding - PYTHON trial

- Multicentrial, RC superiority T early enteral feed vs. oral diet at 72 hour.
- N=208 with APACHE II score ≥8
- Outcome: composite outcome of major infection or death at 6 month
- 30% enteral feeding vs. 27% in on demand group
  - (OR=1.07 CI: 0.79-1.44)
  - Mortality: 11% in EN vs. 7% in oral feeding groups (p=0.33)

Bakker. NEJM. 2014



ERCP in AP

- Patients with AP and concomitant cholangitis should undergo ERCP within 24h of admission
  - Strong recommendation, moderate quality
- ERCP is not needed in most patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction
  - Conditional recommendation, low quality
- In absence of cholangitis and/or jaundice, MRCP or EUS should be used to screen for CBD stone if highly suspected
  - Conditional recommendation, low quality

Role of Antibiotics

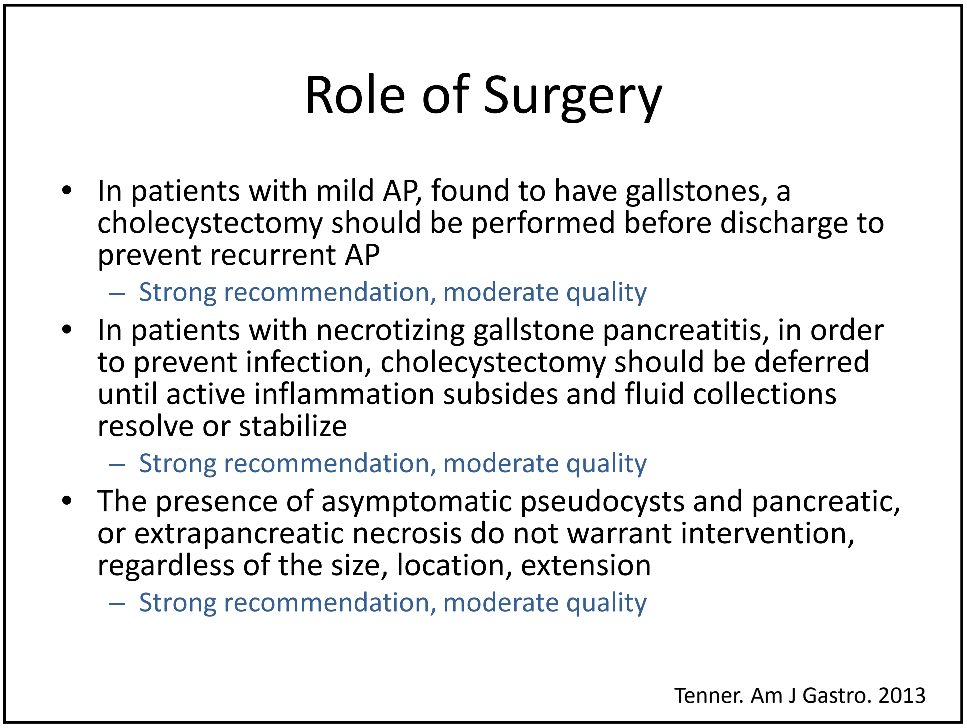
- Should be given for an extrapancreatic infection such as cholangitis
  - Strong recommendation, high quality
- Routine use of prophylactic antibiotics in patients with severe acute pancreatitis is not recommended
  - Strong recommendation, moderate quality

Tenner. Am J Gastro. 2013

Infected necrosis

- Infected necrosis should be considered in patients with necrosis who deteriorate or fail to improve after 7-10 days. CT-FNA should be done prior to ATBx if possible
  - Strong recommendation, low quality
- In infected necrosis, the use of antibiotics known to penetrate pancreatic necrosis, such as carbapenem, quinolones, and metronidazole, may be useful in delaying or avoiding intervention
  - Conditional recommendation, low quality
- Routine administration of antifungal along with prophylactic or therapeutic ATBx is not recommended
  - Conditional recommendation, low quality

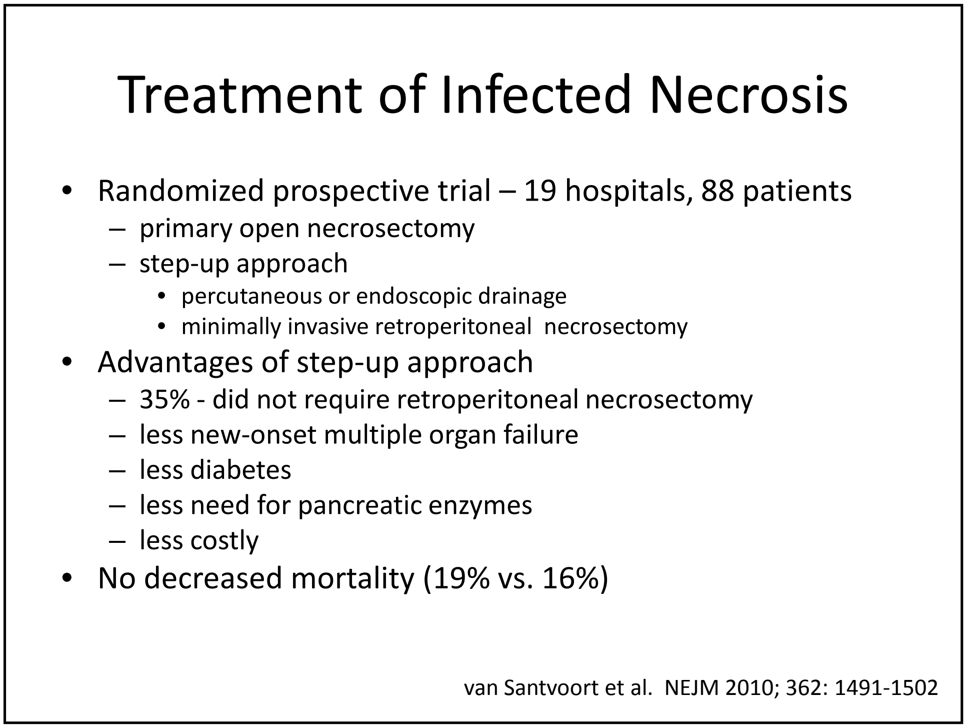
Tenner. Am J Gastro. 2013



Role of Surgery

- In patients with mild AP, found to have gallstones, a cholecystectomy should be performed before discharge to prevent recurrent AP
  - Strong recommendation, moderate quality
- In patients with necrotizing gallstone pancreatitis, in order to prevent infection, cholecystectomy should be deferred until active inflammation subsides and fluid collections resolve or stabilize
  - Strong recommendation, moderate quality
- The presence of asymptomatic pseudocysts and pancreatic, or extrapancreatic necrosis do not warrant intervention, regardless of the size, location, extension
  - Strong recommendation, moderate quality

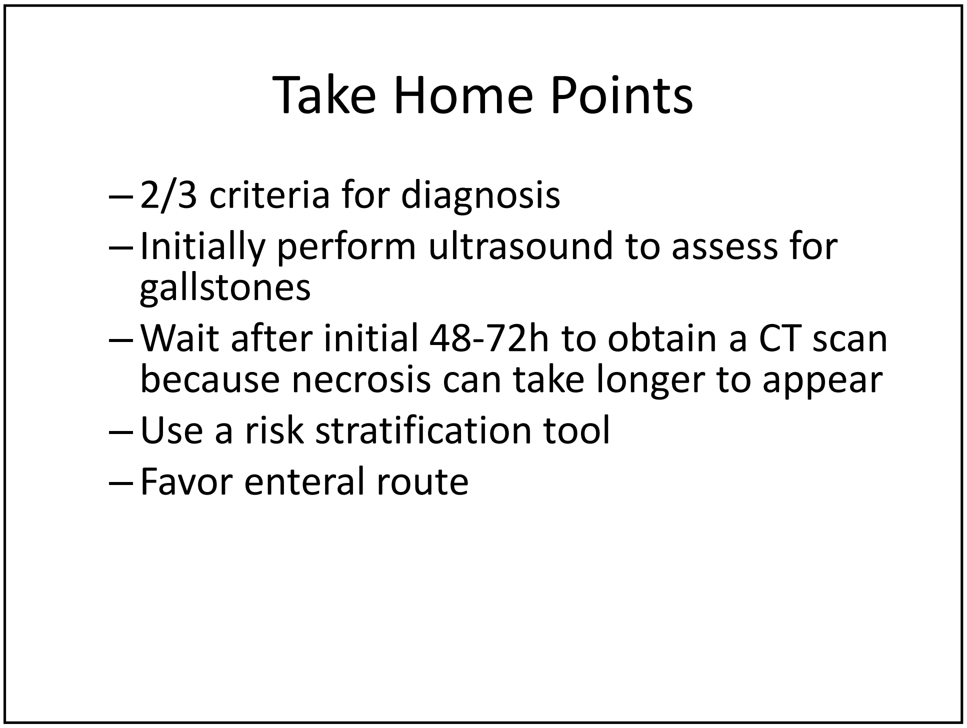
Tenner. Am J Gastro. 2013



Treatment of Infected Necrosis

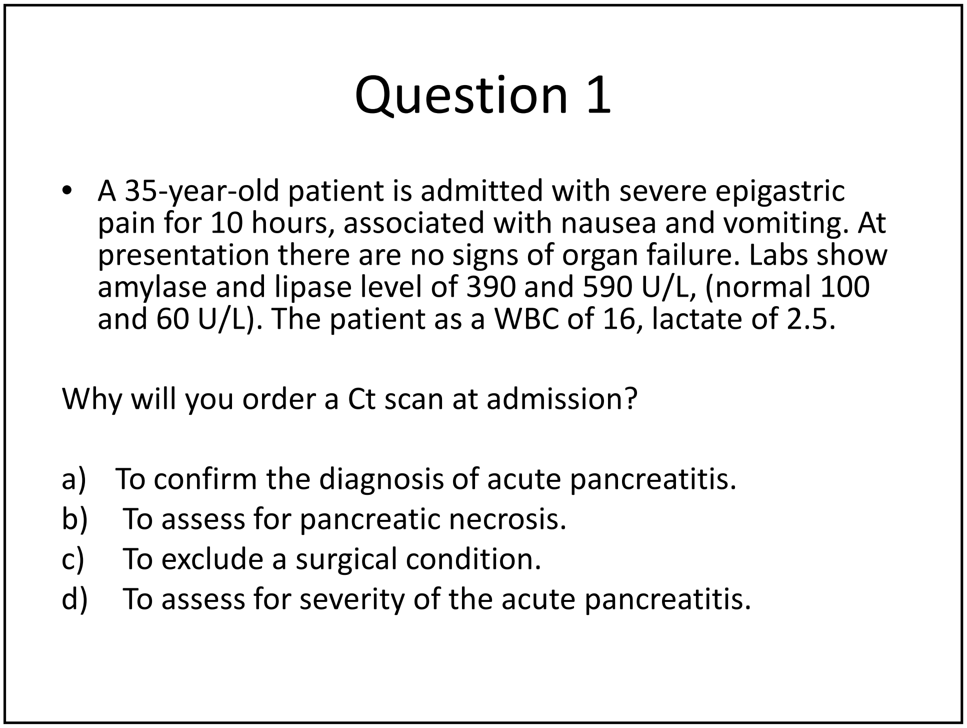
- Randomized prospective trial – 19 hospitals, 88 patients
  - primary open necrosectomy
  - step-up approach
    - percutaneous or endoscopic drainage
    - minimally invasive retroperitoneal necrosectomy
- Advantages of step-up approach
  - 35% - did not require retroperitoneal necrosectomy
  - less new-onset multiple organ failure
  - less diabetes
  - less need for pancreatic enzymes
  - less costly
- No decreased mortality (19% vs. 16%)

van Santvoort et al. NEJM 2010; 362: 1491-1502



Take Home Points

- 2/3 criteria for diagnosis
- Initially perform ultrasound to assess for gallstones
- Wait after initial 48-72h to obtain a CT scan because necrosis can take longer to appear
- Use a risk stratification tool
- Favor enteral route



Question 1

- A 35-year-old patient is admitted with severe epigastric pain for 10 hours, associated with nausea and vomiting. At presentation there are no signs of organ failure. Labs show amylase and lipase level of 390 and 590 U/L, (normal 100 and 60 U/L). The patient as a WBC of 16, lactate of 2.5.

Why will you order a Ct scan at admission?

a) To confirm the diagnosis of acute pancreatitis.
b) To assess for pancreatic necrosis.
c) To exclude a surgical condition.
d) To assess for severity of the acute pancreatitis.

Question 1

- A 35-year-old patient is admitted with severe epigastric pain for 10 hours, associated with nausea and vomiting. At presentation there are no signs of organ failure. Labs show amylase and lipase level of 390 and 590 U/L, (normal 100 and 60 U/L). The patient as a WBC of 16, lactate of 2.5. Why will you order a Ct scan at admission?

a) To confirm the diagnosis of acute pancreatitis.
b) To assess for pancreatic necrosis.
c) To exclude a surgical condition.
d) To assess for severity of the acute pancreatitis.

Early CT or MRI may underestimate the presence of necrosis, the only reason to perform a CT scan is if the diagnosis is unclear, to exclude other diseases.

Question 2

- What is the best fluid type to use for resuscitation in acute pancreatitis?

a) Lactated Ringer
b) Normal saline
c) D5
d) D5 ½ NS

Question 2

- What is the best fluid type to use for resuscitation in acute pancreatitis?

a) Lactated Ringer
b) Normal saline
c) D5
d) D5 ½ NS

The randomized controlled trial by Dr Wu suggested some improvement in SIRS and CRP level with LR.
Wu. Am J Gastro, 2012.

Question 3

- You are caring for a patient with acute necrotizing pancreatitis who is developing worsening sepsis and organ failure despite maximal intensive care and broad spectrum antibiotic administration 12 days after the onset of pancreatitis. You obtain a percutaneous, CT-guided fine needle aspirate of his pancreatic necrosis that demonstrates bacterial infection. The optimal intervention at this time is:

a) Continued antibiotic administration and supportive therapy only
b) Percutaneous drainage
c) Endoscopic transluminal drainage
d) Surgical retroperitoneal debridement

Question 3

- You are caring for a patient with acute necrotizing pancreatitis who is developing worsening sepsis and organ failure despite maximal intensive care and broad spectrum antibiotic administration 12 days after the onset of pancreatitis. You obtain a percutaneous, CT-guided fine needle aspirate of his pancreatic necrosis that demonstrates bacterial infection. The optimal intervention at this time is:

a) Continued antibiotic administration and supportive therapy only
b) Percutaneous drainage
c) Endoscopic transluminal drainage
d) Surgical retroperitoneal debridement

This patient is not responding to antibiotics and needs additional drainage. This is too early to perform an endoscopic necrosectomy. The stepwise approach suggest using percutaneous approach at this time.

van Santvoort et al. NEJM 2010; 362: 1491-1502

References

- Tenner, Baillie, DeWitt. American College of Gastroenterology Guideline: Management of Acute Pancreatitis. Am J Gastro. 2013 Sep;108(9):1400-15; 1416.
- Bakker, van Brunschot, van Santvoort. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. NEJM. 2014 Nov 20;371(21):1983-93.

Acute GI Bleeding

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Assistant Professor of Medicine
Harvard Medical School

Disclosure Slide

Nothing to disclose

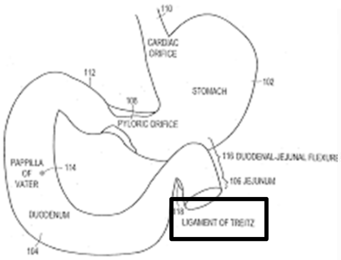
Resuscitate

Upper versus lower GI source?

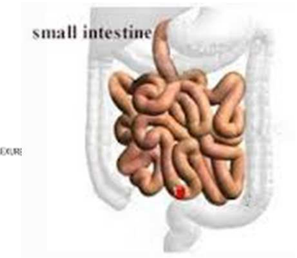
Management

Definitions

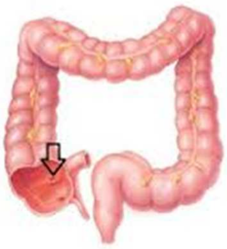
UGIB


110
CARDIAC ORIFICE
112
STOMACH
102
108
PYLORIC ORIFICE
PAPPILLA OF VATER
114
116 DUODENAL-JEJUNAL FLEXURE
106 JEJUNUM
118
LIGAMENT OF TREITZ
DUODENUM
104

Small bowel


small intestine

LGIB

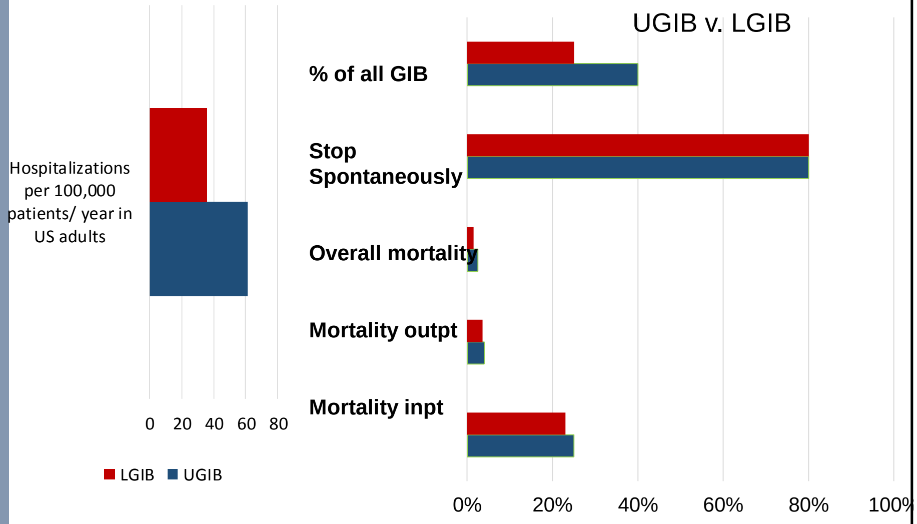


Definitions

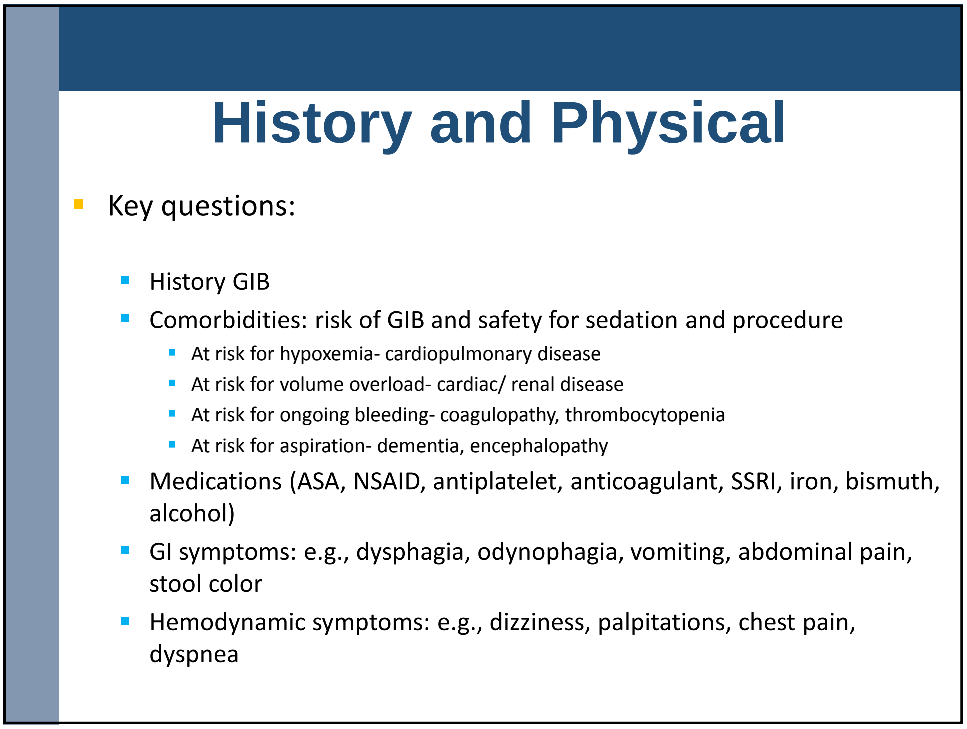
- Occult GIB versus Overt GIB
- Obscure GIB: overt or occult bleeding, no source identified despite EGD and colonoscopy
- Acute: <3 days
- Chronic: slow and/or intermittent blood loss;
  - e.g. occult blood, small amount BRBPR

Wong, GIE 2003; Ghassemi and Jensen. Curr Gastro Rep 2013

Epidemiology

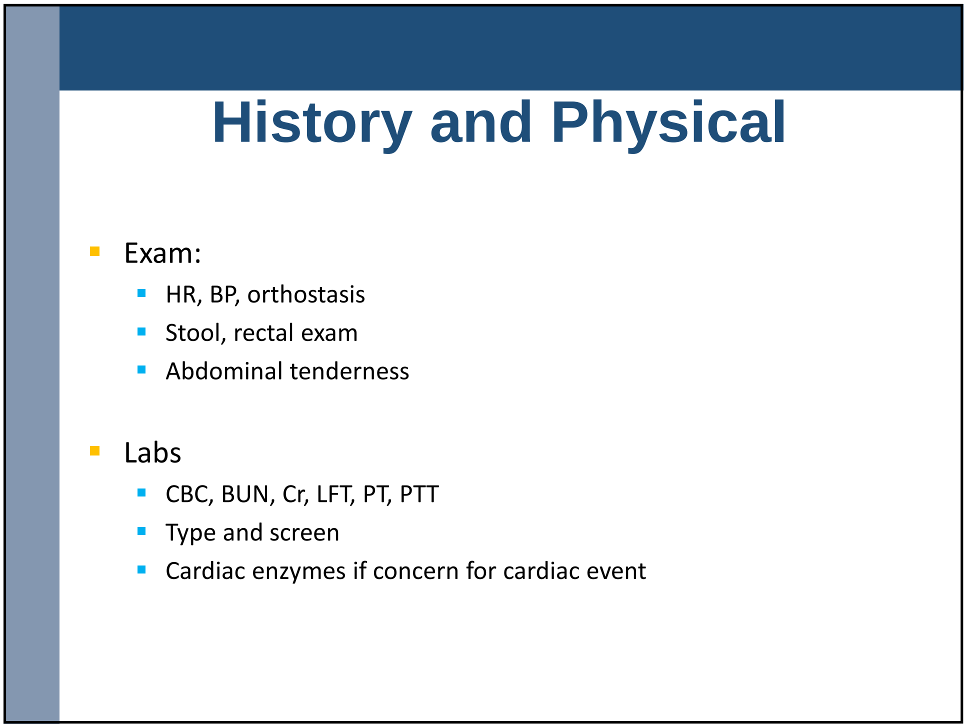


Longstreth. Am J Gastro 1997; Longstreth. Am J Gastro 1995; Laine et al. AJG 2012



History and Physical

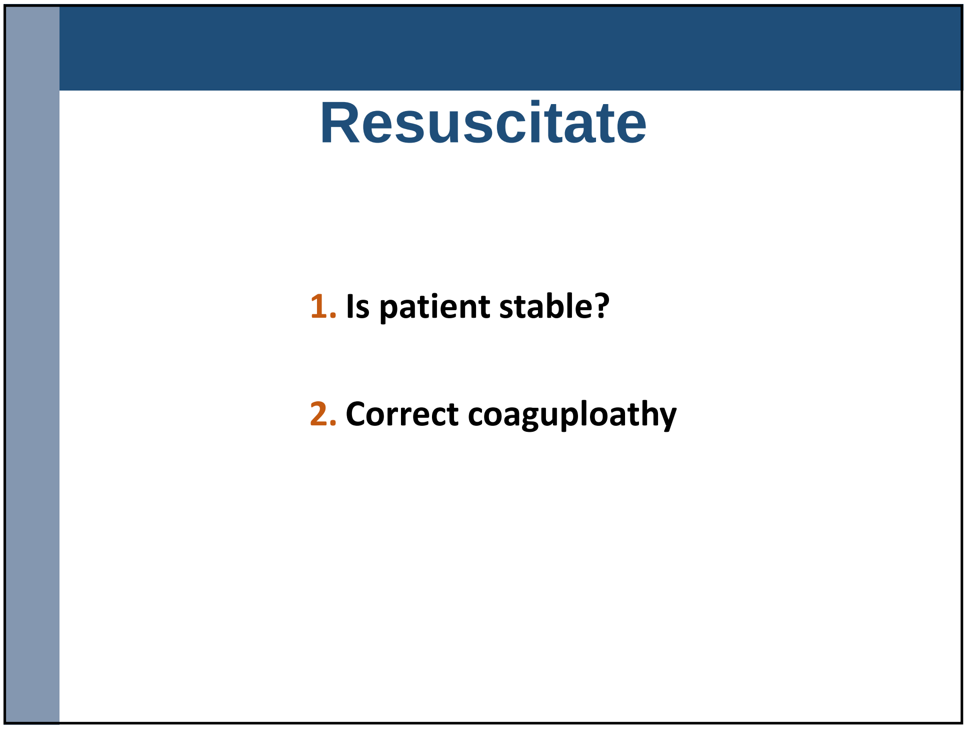
- Key questions:
  - History GIB
  - Comorbidities: risk of GIB and safety for sedation and procedure
    - At risk for hypoxemia- cardiopulmonary disease
    - At risk for volume overload- cardiac/ renal disease
    - At risk for ongoing bleeding- coagulopathy, thrombocytopenia
    - At risk for aspiration- dementia, encephalopathy
  - Medications (ASA, NSAID, antiplatelet, anticoagulant, SSRI, iron, bismuth, alcohol)
  - GI symptoms: e.g., dysphagia, odynophagia, vomiting, abdominal pain, stool color
  - Hemodynamic symptoms: e.g., dizziness, palpitations, chest pain, dyspnea



History and Physical

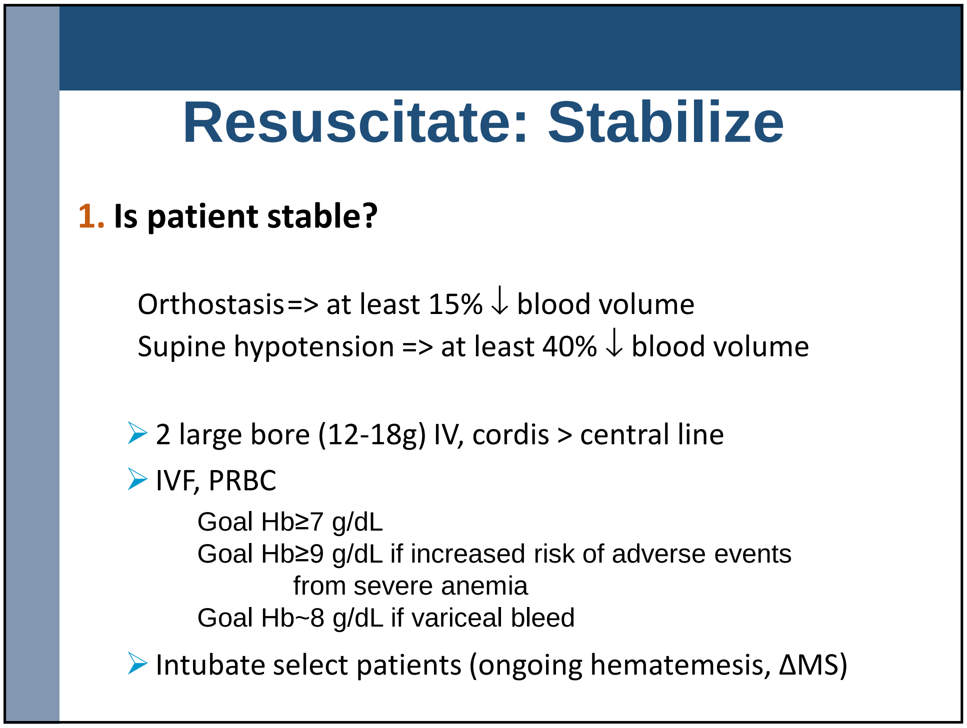
- Exam:
  - HR, BP, orthostasis
  - Stool, rectal exam
  - Abdominal tenderness

- Labs
  - CBC, BUN, Cr, LFT, PT, PTT
  - Type and screen
  - Cardiac enzymes if concern for cardiac event



Resuscitate

1. Is patient stable?
2. Correct coaguploathy



Resuscitate: Stabilize

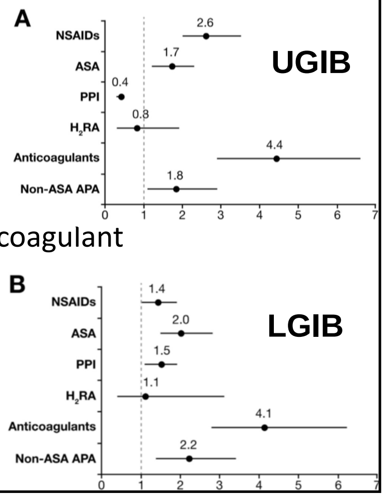
1. Is patient stable?

Orthostasis=> at least 15% ↓ blood volume
Supine hypotension => at least 40% ↓ blood volume

- 2 large bore (12-18g) IV, cordis > central line
- IVF, PRBC
  - Goal Hb≥7 g/dL
  - Goal Hb≥9 g/dL if increased risk of adverse events from severe anemia
  - Goal Hb~8 g/dL if variceal bleed
- Intubate select patients (ongoing hematemesis, ΔMS)

Resuscitate: Correct Coagulopathy

2. **Coagulopathy**



- Goal INR <1.5, plt >50K
- Goal INR <3 before procedure
- Hold ASA, NSAID, antiplatelet, anticoagulant
- ? Hold SSRI
- FFP, vitamin K, kcentra

Lanas et al. CGH 2015; Nagata et al. J Clin Gastro 2015.

Resuscitate: Correct Coagulopathy

FFP

Goal INR <1.5 in active bleeding
Goal <3 before procedure
Every 4u PRBC
Rapid, 3-5h long reversal

FFP

Predicted FFP Volume to Reach Target INR

	Target INR	
	1.5	1.7
Initial INR	Volume (L)	Volume (L)
6.0	3.5	2.5
5.0	3.0	2.3
4.0	2.5	2.0
3.0	2.0	1.5
2.0	1.5	0.5

Resuscitate: Correct Coagulopathy

4-Factor-Prothrombin Complex Concentrate

<30 minutes, INR <1.3
85% less volume than FFP
6X more expensive

Resuscitate: Correct Coagulopathy

Vitamin K

IV: major bleed
anaphylaxis, unclear if dose-related

Dose unclear
- Usually 5mg

Timing: 12-24h for full effect, IV faster

Severity GIB

- Identify high risk patients → triage care
- Identify low risk patients → early discharge
- Validated scoring systems predict rebleed, surgery, mortality
  - UGIB: Rockall, Blatchford, BLEED
  - LGIB: few studies

Rockall et al. Lancet 1996;347:1138.
Blatchford et al. Lancet 2000;356:1318.
Kollef et al. Crit Care Med 1997;25:1125.
Imperiale et al. Arch Intern Med 2007;167:1291.
Strate et al. CGH 2008.

Predictors of Mortality

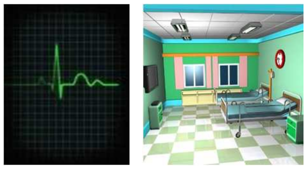
- Age>60
- Comorbidity
- SBP<100, HR>100
- Stool: BRBPR, melena
- Hemoglobin <10
- Inpatient
- Intestinal ischemia

Endoscopic stigmata
Variceal bleeding

Admission

ΔMS,
Unstable

Otherwise,

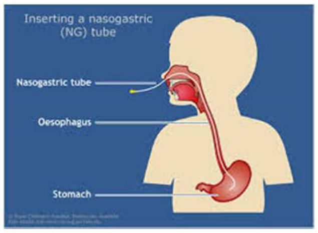


UGI vs. LGIB

- 10-20% initially 'LGIB' have UGI source
- Clues to UGIB: hematochezia with hemodynamic instability, melena by history or exam, h/o UGIB, elevated BUN
- BUN/Cr >30 => UGIB
- Clots in stool=> LGIB

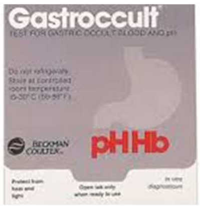
Srygley et al. JAMA 2012.
Laine et al. AJG 2010.

UGI vs. LGIB: NGT?


Inserting a nasogastric (NG) tube
Nasogastric tube
Oesophagus
Stomach

	Sensitivity	Specificity
NGT aspirate to predict UGIB	42-84%	55%

NGT v. no NGT: No difference in mortality, transfusions, surgery, LOS


Gastroccult
TEST FOR GASTRIC OCCULT BLOOD AND pH
BECKMAN COULTER
pH Hb

	Sensitivity	Specificity
Gastroccult	96%	18%

- Positive=> FALSE POSITIVE
- Negative=> TRUE NEGATIVE

Huang ES et al. GIE 2011.

UGI vs. LGIB: NGT?

Inserting a nasogastric
(NG
Nasogastric tub
Oesophagu
Stomac

	Sensitivity	Specificity
NGT aspirate to predict UGIB	42-84%	55%

NGT v. no NGT: No difference in mortality, transfusions, surgery, LOS

	Sensitivity	Specificity
Gastroccult	96%	18%

- Positive=> FALSE POSITIVE
- Negative=> TRUE NEGATIVE

Huang ES et al. GIE 2011.

Management UGIB: Nonvariceal

Nonvariceal UGIB Differential Diagnosis

- PUD 30-56%
- Mallory-Weiss tear 15-20%
- Erosive gastritis, duodenitis 10-15%
- Esophagitis 5-10%
- AVM 5%
- Dieulafoy 2%
- Neoplasm 1-2%
- Other 5%: GAVE, Cameron ulcer

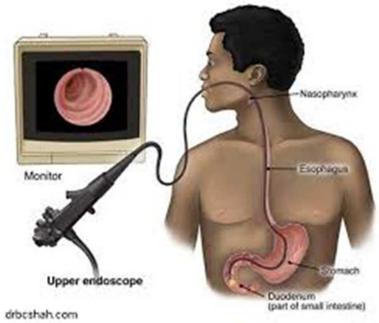
Pre-EGD Management UGIB: Nonvariceal

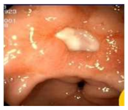
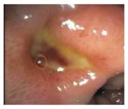
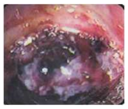
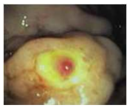
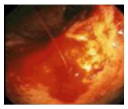
IV PPI 80mg bolus,
8mg/h or IV BID

Consider IV erythromycin 3mg/kg 30-90 min before EGD

Hwang JH et al. GIE 2012.
Sreedharan A et al. Cochrane Data 2010.

Endoscopy


Monitor
Upper endoscope
drbcshah.com
Nasopharynx
Esophagus
Stomach
Duodenum
(part of small intestine)

	Endoscopic stigmata	% Rebleed	
	Clean-based ulcer	<3%	Low risk
	Pigmented flat spot	<8%	
	Adherent clot	8-35%	High risk
	Nonbleeding visible vessel	50%	
	Active bleeding	Near 100%	

Laine et al. NEJM 1994;33:717.

Endoscopic Therapy

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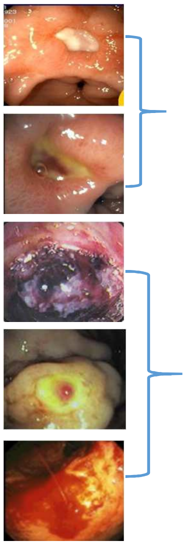
Post-EGD Management
Nonvariceal UGIB



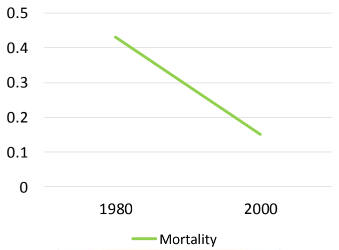
Feed and discharge
PO PPI QD with appropriate follow-up per GI
Check H pylori

Watch for 72 hrs
IV PPI BID x72 hrs

Laine L et al. JAMA 2014.
Hwang JH et al. GIE 2012.
Barkun A et al. Ann Int Med 2010.

Management UGIB: Variceal

Early Management Variceal UGIB



- 1st 14d after bleeding crucial
  - Most inpatient deaths due to rebleeding
- Resuscitation
  - Consider intubation
  - Do NOT over transfuse
  - Goal Hb ~8
- EGD within 12 hours

Early Management Variceal UGIB: Medications

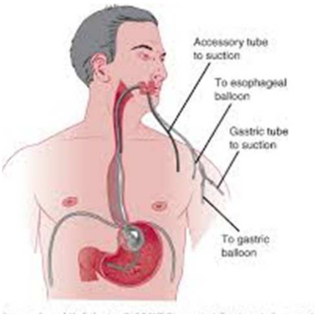
Octreotide

- ↓ rebleed
- 50-100mcg IV bolus → 50mcg/h x3-5d

Antibiotics

- ↓ mortality and infection
- Quinolone IV/PO or ceftriaxone 1gm IV QD x 7 days

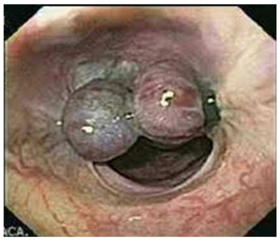
Early Management Variceal UGIB: Balloon Tamponade


Accessory tube to suction
To esophageal balloon
Gastric tube to suction
To gastric balloon

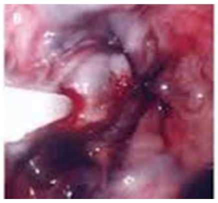
24h bridge to definitive therapy with EGD, TIPS, and/ or surgery

Initial success 30-90%

Definitive Management Variceal UGIB: EGD



Endoscopic variceal ligation



Endoscopic sclerotherapy

Summary Early Management UGIB Before EGD

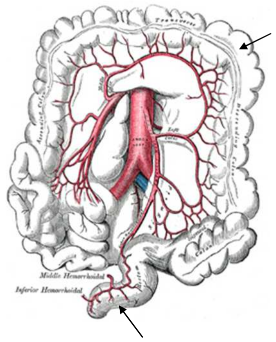
- Nonvariceal UGIB
  - Goal Hb >7 or 9
  - INR < 1.5 (INR < 3 pre-procedure), plt > 50K
  - IV PPI infusion or IV BID
  - Consider IV erythromycin
  - Hold all ASA/NSAIDS/ blood thinning agents, if possible
- Variceal UGIB
  - Do not over transfuse, goal Hb ~8
  - Intubate
  - ASAP IV fluoroquinolone/ ceftriaxone x7d
  - ASAP IV octreotide 50mcg bolus→ 50mcg/h x3-5d

Lower GI Bleed

Differential Diagnosis

- Diverticulosis 20-65%
- Neoplasia 1-17%
- Ischemic colitis 1-19%
- Angiodysplasia 3-15%
- Hemorrhoids 5-10%
- Postpolypectomy 2-6%
- IBD
- Infectious colitis
- NSAID
- Radiation
- Dieulafoy’s, rectal varices, stercoral ulcer
- Small bowel (e.g. aortoenteric fistula, Meckel’s) 2-15%
- UGI source 11-15%
- Unknown 12%

Differential Diagnosis


Middle Hemorrhoidal
Inferior Hemorrhoidal

- Diverticulosis 20-65%
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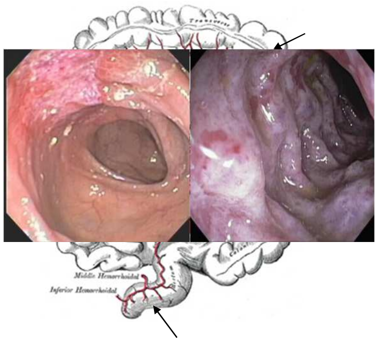
Differential Diagnosis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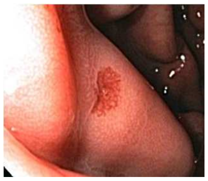
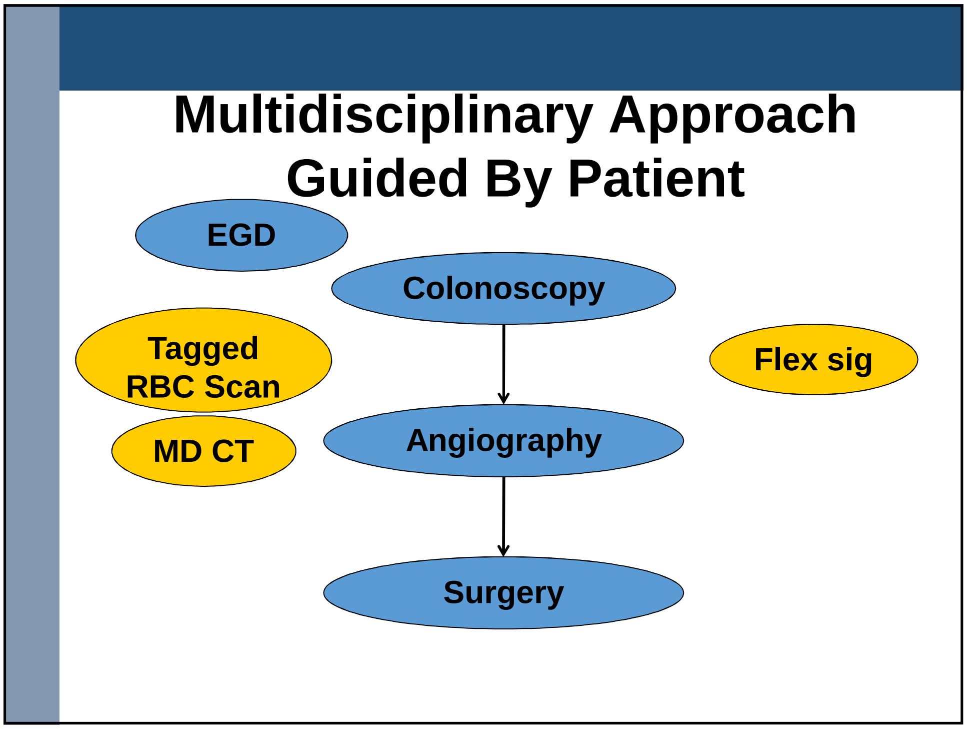


Procedures in LGIB

	Diagnostic yield	Therapy	Complications
Colonoscopy	45-100%	10-40%	<2%
Tagged RBC scan	40-70%	-	-
CT angiography	45-100%	-	-
Angiography	35-86%	-	17%

ASGE guideline. GIE 2014.
Strate LL et al. CGH 2010.



Multidisciplinary Approach Guided By Patient

EGD

Colonoscopy

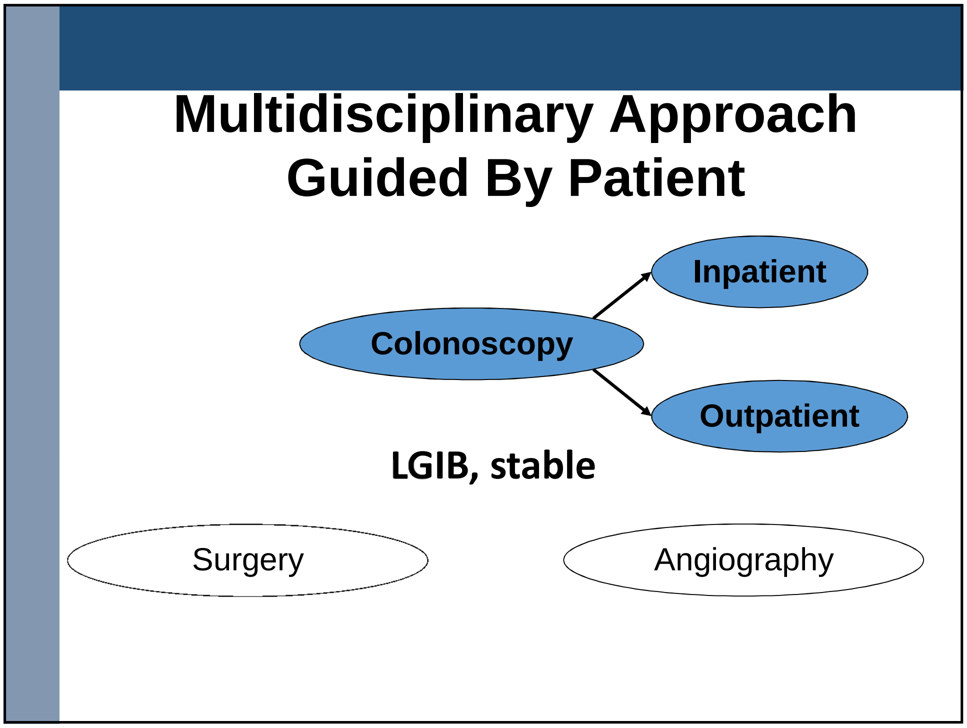
Tagged RBC Scan

Flex sig

MD CT

Angiography

Surgery



Multidisciplinary Approach Guided By Patient

Inpatient

Colonoscopy

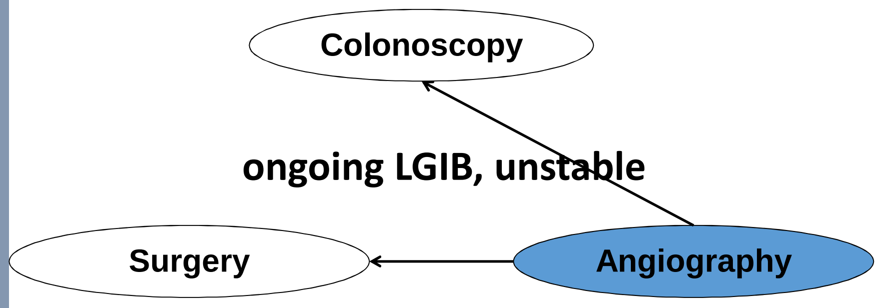
Outpatient

LGIB, stable

Surgery

Angiography

Multidisciplinary Approach Guided By Patient



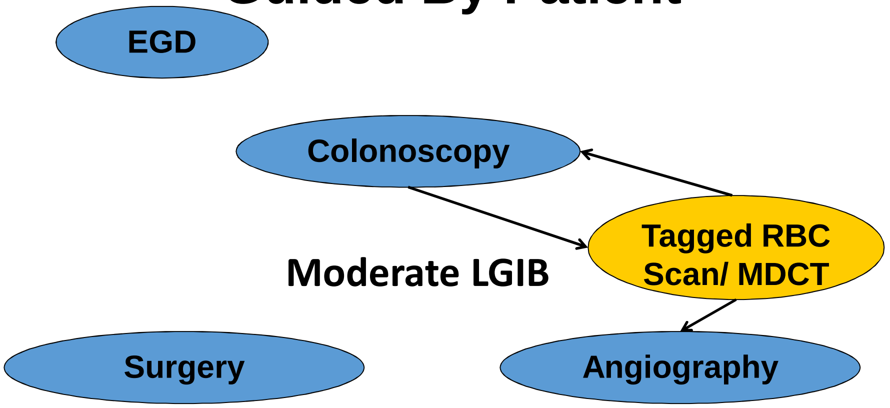
Colonoscopy

ongoing LGIB, unstable

Surgery

Angiography

Multidisciplinary Approach Guided By Patient



EGD

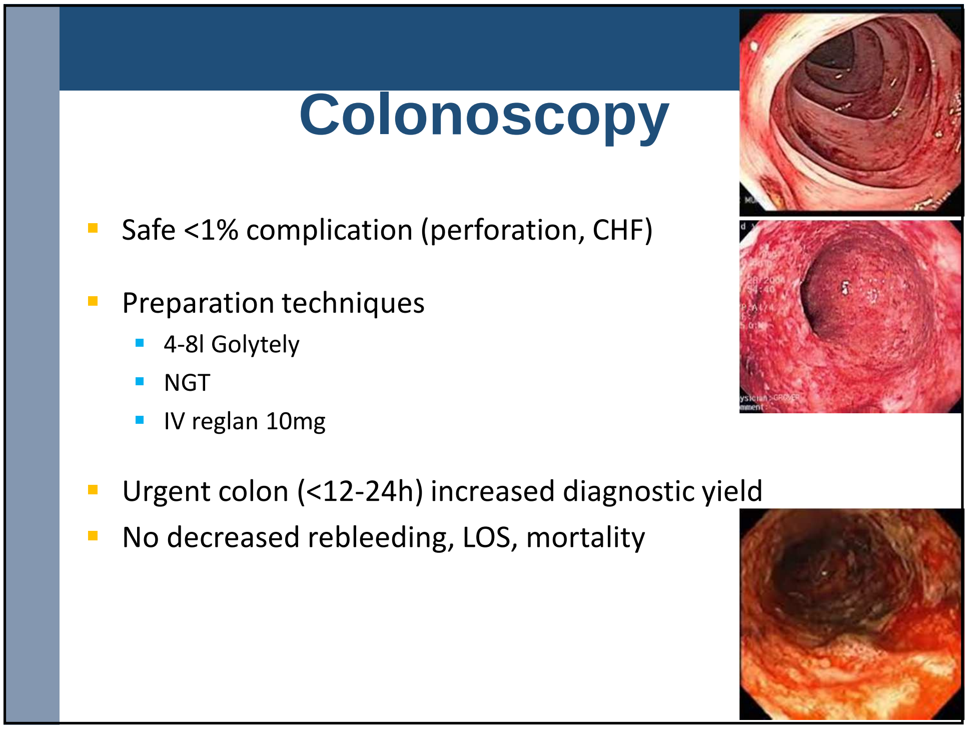
Colonoscopy

Tagged RBC Scan/ MDCT

Moderate LGIB

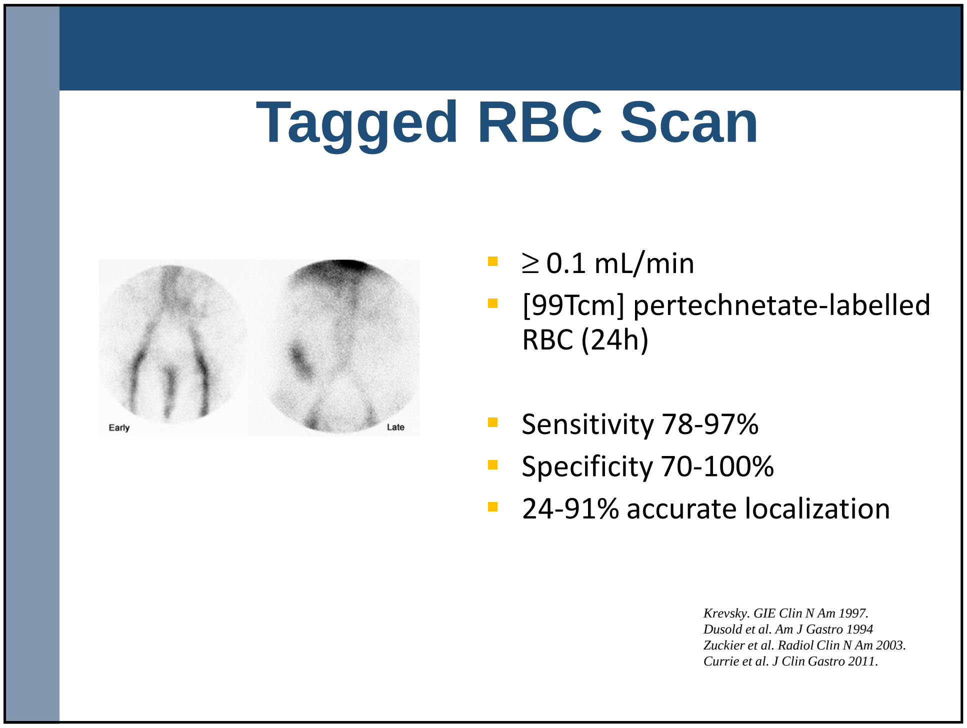
Surgery

Angiography



Colonoscopy

- Safe <1% complication (perforation, CHF)
- Preparation techniques
  - 4-8l Golytely
  - NGT
  - IV reglan 10mg
- Urgent colon (<12-24h) increased diagnostic yield
- No decreased rebleeding, LOS, mortality



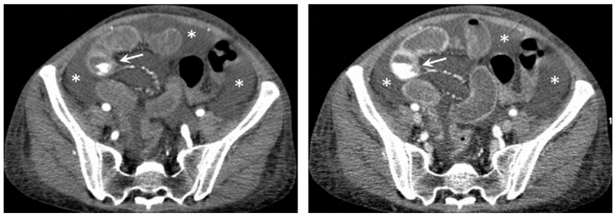
Tagged RBC Scan

- ≥ 0.1 mL/min
- [99Tcm] pertechnetate-labelled RBC (24h)
- Sensitivity 78-97%
- Specificity 70-100%
- 24-91% accurate localization

Krevsky. GIE Clin N Am 1997.
Dusold et al. Am J Gastro 1994
Zuckier et al. Radiol Clin N Am 2003.
Currie et al. J Clin Gastro 2011.

MDCT (CT Angiography)

≥ 0.3-0.5 mL/min



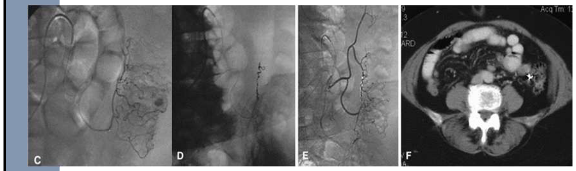
GIB	Sensitivity for Detecting Source of Bleeding
Active bleeding	91-92%
Obscure GI bleeding	45-47%

Specificity 92-95%
Increase diagnostic yield of colonoscopy by 15%
Likely more accurate for detecting and localizing than tagged RBC

Marti et al. Radiology 2012; Geffroy et al. Radiographics 2011; Chan et al. Cardio Int Rad 2014; Nagata et al. J GI 2015; Fuerstein et al. AJR 2016.

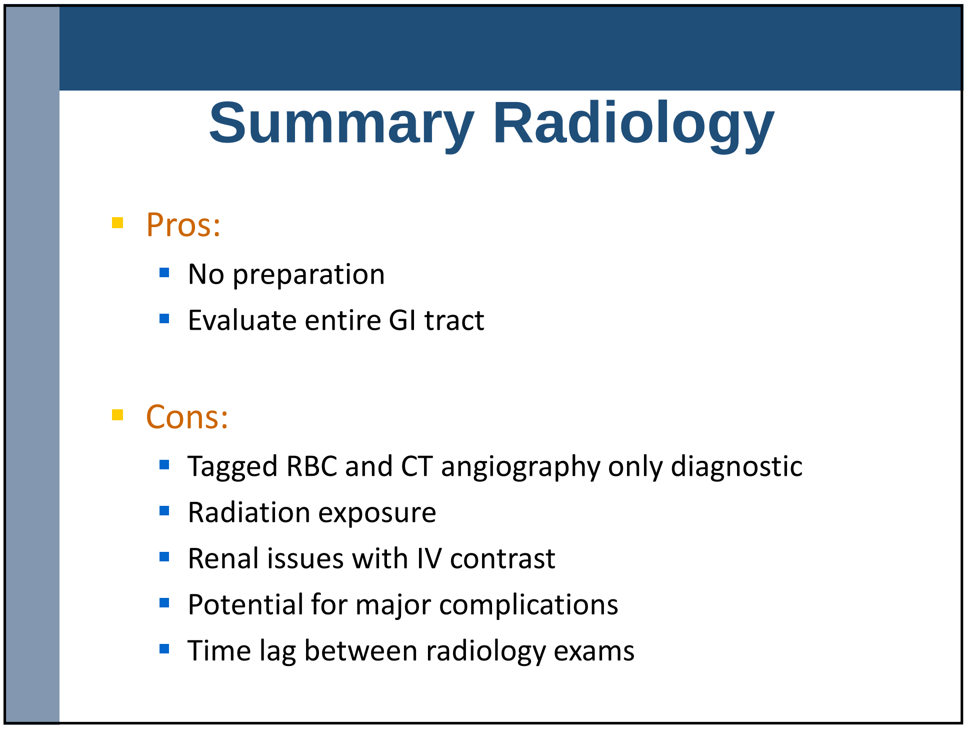
Angiography

Superselective microcatheter



- ≥ 1 mL/min
- Ideally within 1h positive tagged RBC scan
- Angiography w/o scan:
  - Hemodynamically unstable
  - Severe bleeding
- 60% sensitivity, 100% specificity
- 17% major complication (surgery, death)

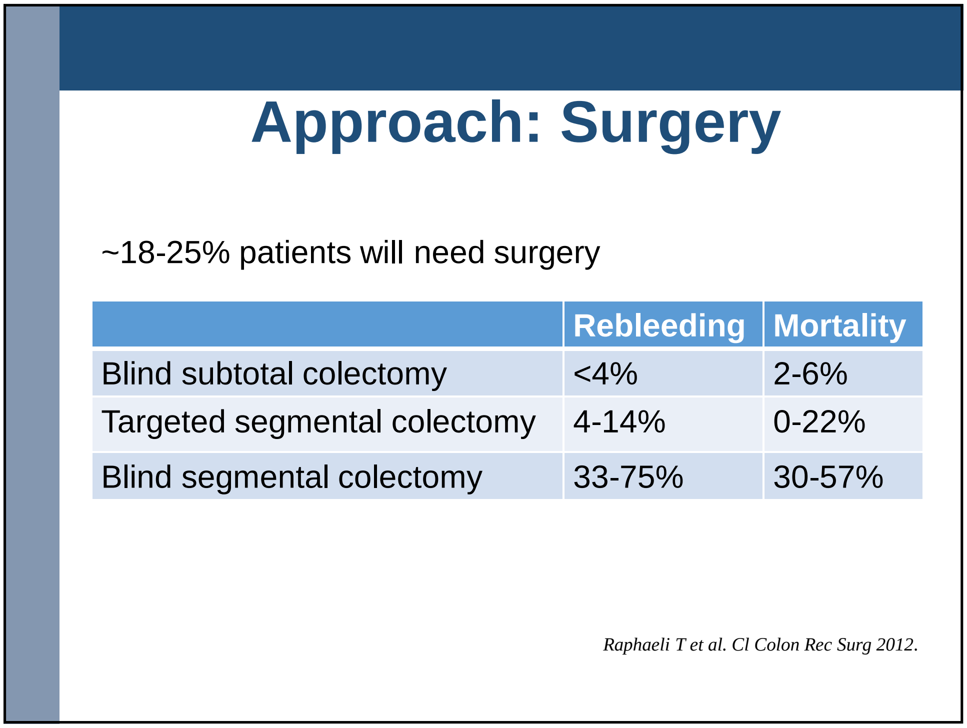
Funaki. Abd Imaging 2004.
DeBarros et al. Dis Colon Rectum 2002.
Maleux et al. Am J Gastro 2009.



Summary Radiology

- Pros:
  - No preparation
  - Evaluate entire GI tract

- Cons:
  - Tagged RBC and CT angiography only diagnostic
  - Radiation exposure
  - Renal issues with IV contrast
  - Potential for major complications
  - Time lag between radiology exams



Approach: Surgery

~18-25% patients will need surgery

	Rebleeding	Mortality
Blind subtotal colectomy	<4%	2-6%
Targeted segmental colectomy	4-14%	0-22%
Blind segmental colectomy	33-75%	30-57%

Raphaeli T et al. Cl Colon Rec Surg 2012.

Approach

- Low risk LGIB, stable:
  - Prep for colonoscopy
  - Consider outpt exam in only select patients
- Severe LGIB, unstable:
  - Exclude upper GI source
  - Angiography
  - Consider surgery
- Ongoing LGIB, stable, unprepped:
  - Start prep
  - Consider upper GI source
  - Tagged RBC scan/ MDCT

Conclusions

- Resuscitate with at least 2 large bore IV
- Transfuse to appropriate goal Hb
- Correct coagulopathy with FFP, vitamin K, kcentra
- UGI versus LGI source?
- Nonvariceal UGIB,
  - ➢ IV PPI drip or BID pre-EGD
  - ➢ EGD within 24 hours

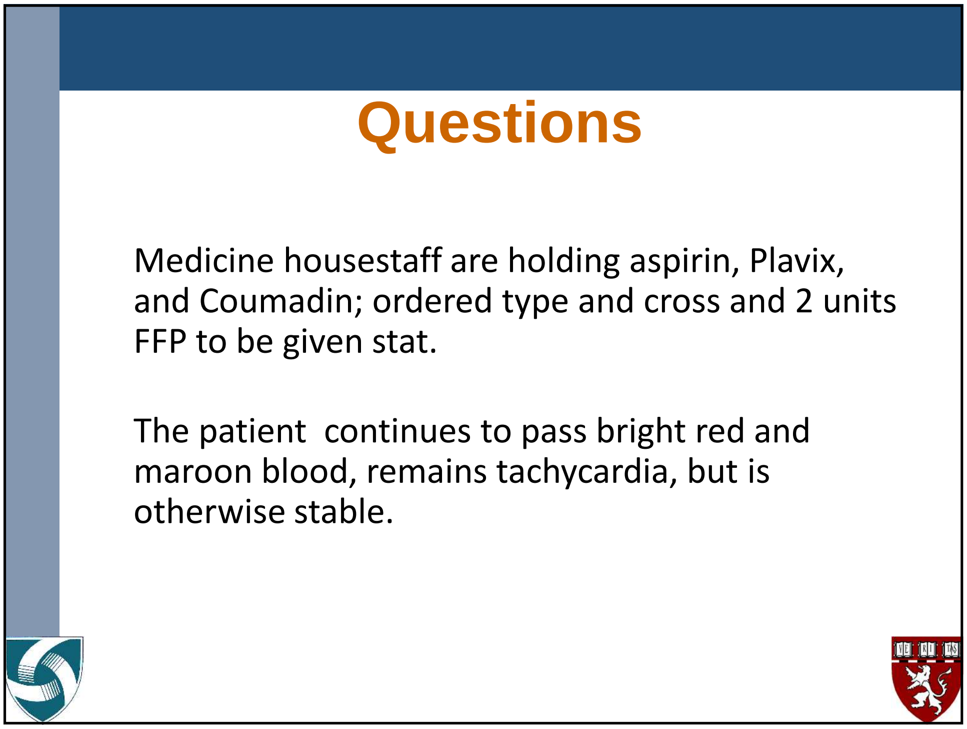
Conclusions

- Variceal UGIB, IV antibiotics, octreotide
  - Consider intubation
  - EGD within 12 hours
- LGIB: Multidisciplinary approach tailored to patient
- Colonoscopy within 12-24h
- Angiography for severe unstable bleeding
- Tagged RBC or CT angiography with less severe, but ongoing bleed and not prepped

Questions

1. A 77yo male with history of MI and atrial fibrillation on aspirin, Plavix, and Coumadin and chronic renal insufficiency presents with BRBPR. He has had about 5 bloody bowel movements, feels lightheaded, and denies abdominal pain, nausea or vomiting. He has no history of GIB and never had a colonoscopy.

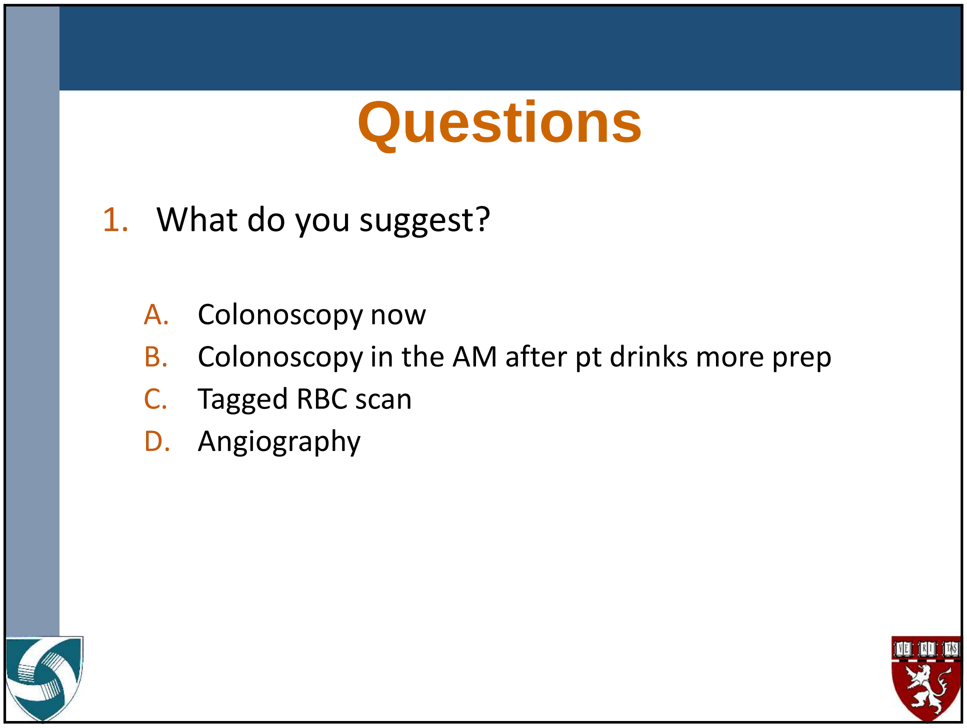
Exam: HR 102, BP 105/72
Rectal: bright red blood on glove, no stool
Hct 29, plt 220, INR 6



Questions

Medicine housestaff are holding aspirin, Plavix, and Coumadin; ordered type and cross and 2 units FFP to be given stat.

The patient continues to pass bright red and maroon blood, remains tachycardia, but is otherwise stable.



Questions

1. What do you suggest?

   A. Colonoscopy now
   B. Colonoscopy in the AM after pt drinks more prep
   C. Tagged RBC scan
   D. Angiography

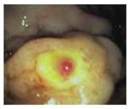
Questions

1. Answer: C Tagged RBC scan

   Most likely the patient is having lower GI bleeding although upper GI bleeding is possible given his aspirin use. Colonoscopy now is not feasible as the patient is not prepared and has an INR of 6, which should be less than 3 before doing a procedure. While the patient can start drinking preparation for anticipated colonoscopy in 12-24 hours, he is continuing to pass bloody bowel movements now. This implies ongoing active bleeding that is likely at a pace rapid enough to be detected by tagged RBC scan. Therefore, he should undergo this study before angiography to help localize the bleeding source especially given his chronic renal insufficiency.

Questions

2. 45 year old male with a past medical history of hypertension, coronary artery disease s/p cardiac cath with stent placement on ASA and clopidogrel presents with melena. EGD reveals the following:



What medical therapy should occur after EGD treatment of this lesion?

A. Nothing

B. IV PPI continuous infusion for 72 hours

C. IV PPI BID for 72 hours

D. PO PPI BID for 72 hours

Questions

2. Answer: C IV PPI BID for 72 hours

A recent meta-analysis concluded that the risk of rebleeding in patients with high-risk ulcers (bleeding, nonbleeding visible vessel, or adherent clot) that were successfully treated endoscopically was comparable for patients placed on intermittent PPI versus continuous PPI infusion.

Questions

3. 42yo female with alcoholic cirrhosis and history of esophageal variceal bleeding presents with hematemesis and hypotension.

Which of the following should occur even before EGD?

A. Transfuse for goal hemoglobin > 10 g/dL
B. IV PPI bolus and infusion
C. IV octreotide bolus and infusion
D. IV meropenem

Questions

3. Answer: C IV octreotide bolus and infusion

Although IV octreotide has not been proven to decrease mortality in variceal bleeding, it does reduce rebleeding. Prophylactic antibiotics have been shown to reduce mortality in variceal bleeding but include specifically quinolones or ceftriaxone in areas with high resistance to quinolones and potentially advanced cirrhotics. Transfusion goal in variceal bleeding is modest with goal hemoglobin approximately 8 g/dL.

References

1. Hwang JH et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc 2014;80:221-7.
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Acute Liver Failure

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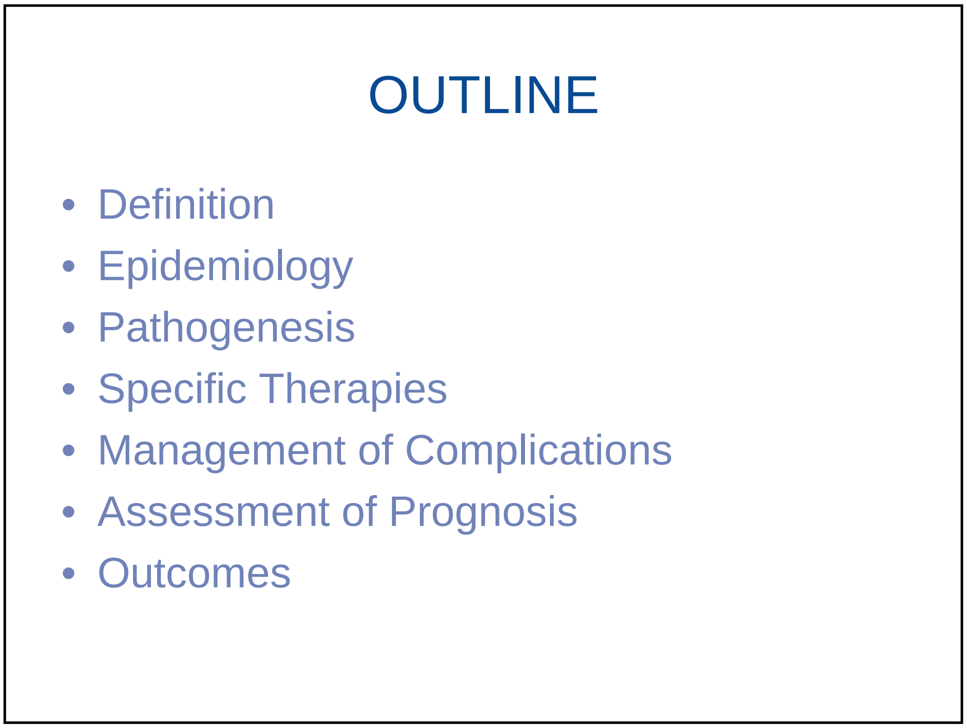
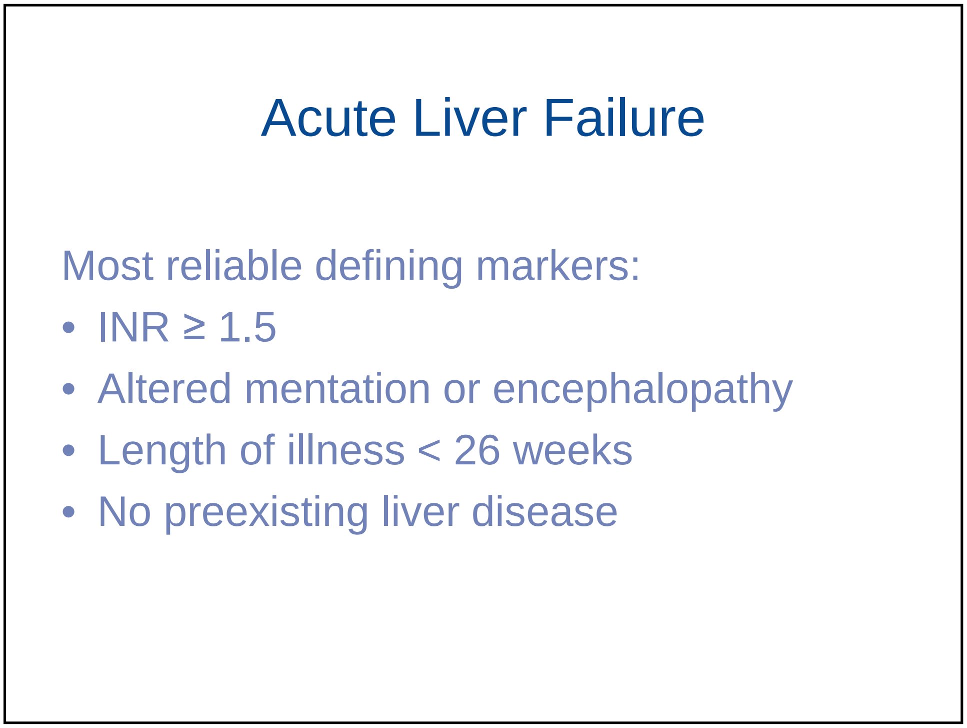
I have no disclosures relevant to this presentation.



OUTLINE

- Definition
- Epidemiology
- Pathogenesis
- Specific Therapies
- Management of Complications
- Assessment of Prognosis
- Outcomes



Acute Liver Failure

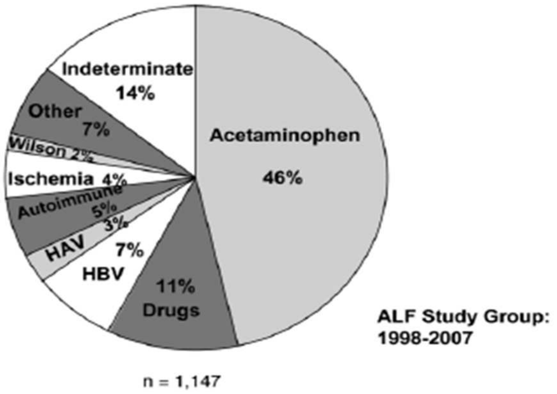
Most reliable defining markers:

- INR ≥ 1.5
- Altered mentation or encephalopathy
- Length of illness < 26 weeks
- No preexisting liver disease

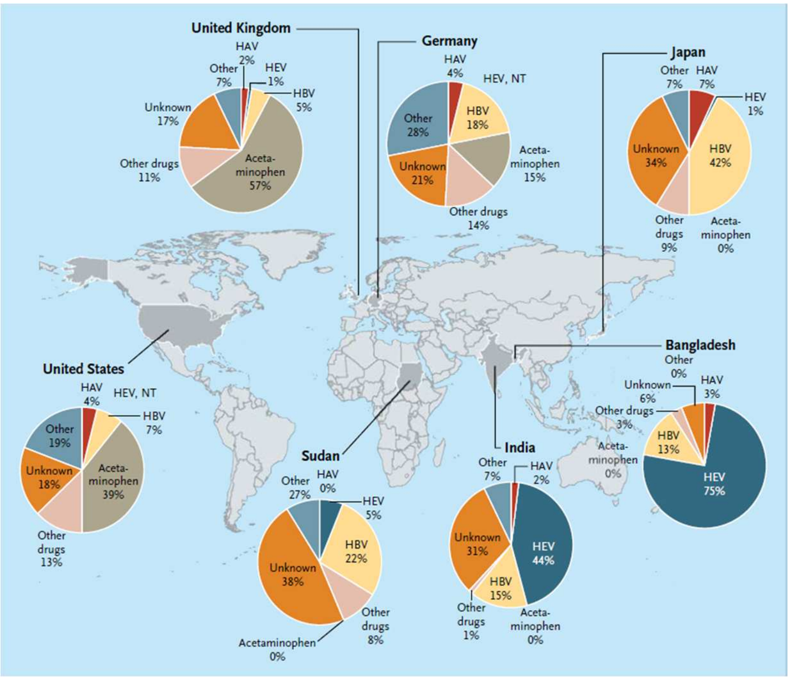
Background on ALF

- Rare: ~2,000 cases/year in U.S.
- No one medical center can study the condition
- Variety of etiologies
- No viable treatment for all patients
- Morbidity/mortality 94% prior to transplant
- Patients can be listed UNOS Status 1 for 7 days
- Prior to 1980's, HBV was >40% cases

Etiology of ALF in Adults in United States



Hepatology 2008; 47: 1401-1415.


United Kingdom
HAV 2%
Other 7%
HEV 1%
HBV 5%
Unknown 17%
Other drugs 11%
Aceta-minophen 57%
Germany
HAV 4%
HEV, NT
Other 28%
HBV 18%
Unknown 21%
Aceta-minophen 15%
Other drugs 14%
Japan
Other 7%
HAV 7%
HEV 1%
Unknown 34%
HBV 42%
Other drugs 9%
Aceta-minophen 0%
United States
HAV 4%
HEV, NT
HBV 7%
Other 19%
Unknown 18%
Aceta-minophen 39%
Other drugs 13%
Bangladesh
Other 0%
Unknown 6%
HAV 3%
Other drugs 3%
HBV 13%
Aceta-minophen 0%
HEV 75%
Sudan
Other 27%
HAV 0%
HEV 5%
HBV 22%
Unknown 38%
Other drugs 8%
Acetaminophen 0%
India
Other 7%
HAV 2%
Unknown 31%
HEV 44%
HBV 15%
Other drugs 1%
Aceta-minophen 0%

NEJM 2013; 369: 2528.

Etiology and Clinical Characteristics of ALF

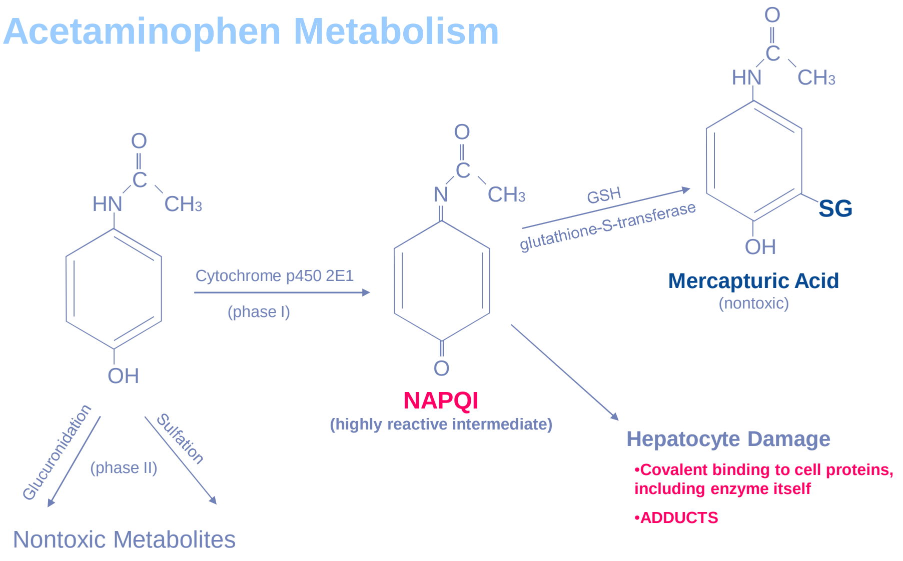
	Acetaminophen	Drugs	Indeterminate	Hep A	Hep B	All Others
Median Age	37	46	38	47	42	42
Female Sex	76%	67%	58%	45%	42%	76%
Jaundice to Coma (Days)	0	9	9	3	7	7
Coma ≥ 3	52%	38%	50%	55%	54%	41%
Median ALT	4067	600	847	2404	1707	650
Median Bilirubin	4.5	20.2	23.0	11.9	19.7	15.3
Transplant Free Survival	65%	29%	25%	58%	25%	34%
Transplant	9%	41%	43%	29%	47%	33%
Death	26%	31%	32%	13%	28%	33%

Hepatology 2008; 47: 1401-1415

Acetaminophen: Scope of Problem

- Billion dollar problem: OTC, > 300 brands
- Unique dose-related toxicity
- 100,000 calls to Poison Control annually
- 50,000 ER visits/year
- 10,000 hospitalizations/year
- ~100-500 deaths/year
- Hydrocodone/APAP is number 1 generic prescription drug – >100 million prescriptions/year (Lorcet, Lortab, Maxidone, Vicodin, Zydone)
- Since 1998 Britain has limited package size to 16-24 and employed blister packs → decreased complications by 27-33% (hospital admissions, transplants, deaths)
- FDA advisory committee recommendations (2009) starting to be administered

Acetaminophen Metabolism


O
C
HN
CH3
OH
Cytochrome p450 2E1
(phase I)
O
C
N
CH3
O
GSH
glutathione-S-transferase
O
C
HN
CH3
SG
OH
Glucuronidation
(phase II)
Sulfation

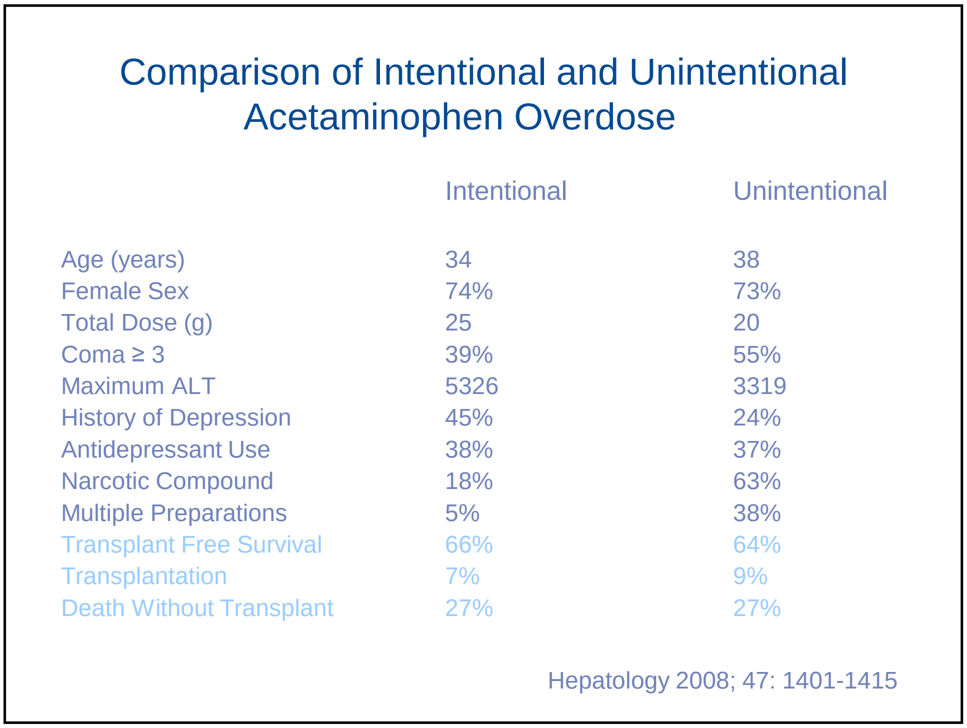
Mercapturic Acid
(nontoxic)

NAPQI
(highly reactive intermediate)

Nontoxic Metabolites

Hepatocyte Damage

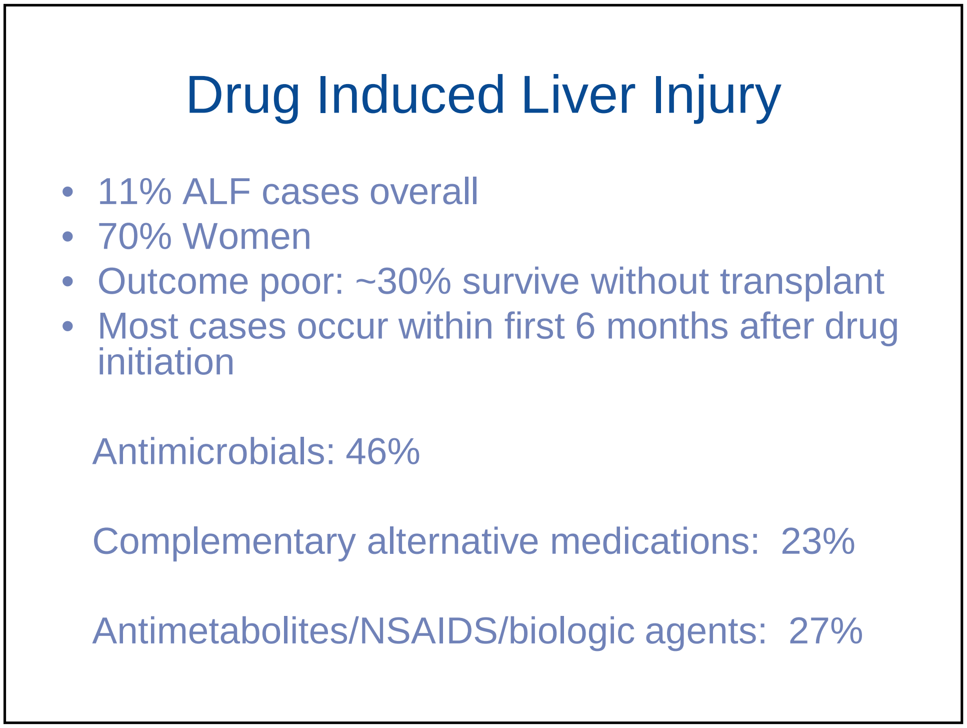
- **Covalent binding to cell proteins, including enzyme itself**
- **ADDUCTS**



Comparison of Intentional and Unintentional Acetaminophen Overdose

	Intentional	Unintentional
Age (years)	34	38
Female Sex	74%	73%
Total Dose (g)	25	20
Coma ≥ 3	39%	55%
Maximum ALT	5326	3319
History of Depression	45%	24%
Antidepressant Use	38%	37%
Narcotic Compound	18%	63%
Multiple Preparations	5%	38%
Transplant Free Survival	66%	64%
Transplantation	7%	9%
Death Without Transplant	27%	27%

Hepatology 2008; 47: 1401-1415



Drug Induced Liver Injury

- 11% ALF cases overall
- 70% Women
- Outcome poor: ~30% survive without transplant
- Most cases occur within first 6 months after drug initiation

Antimicrobials: 46%

Complementary alternative medications: 23%

Antimetabolites/NSAIDS/biologic agents: 27%

Drug Induced Liver Injury

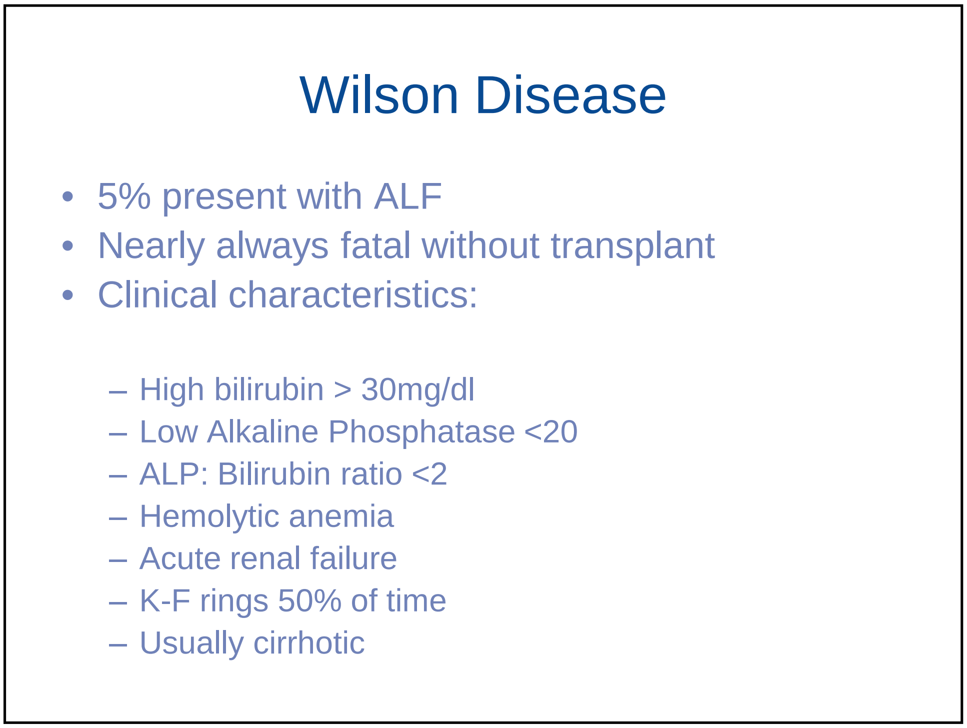
http://livertox.nlm.nih.gov – DILIN network

Isoniazid
Sulfasalazine
Phenytoin
Statins
Propylthiouracil
Ciprofloxacin
Nitrofurantoin
Cocaine
Valproic Acid
Amiodarone
Dapsone
Didanosine
Efavirenz
Carbamazepine
MDMA (Ecstasy)
Labetalol

Itraconazole
Nicotinic Acid
Ketoconazole
Doxycycline
Diclofenac
Trimethoprim-Sulfa
Rifampin-Isoniazid
Amoxicillin-Clavulanate
Kava Kava
Herbalife
Hydroxycut
Comfrey
Senecio
Greater celandine
He Shon Wu
LipoKinetix
Ma Huang

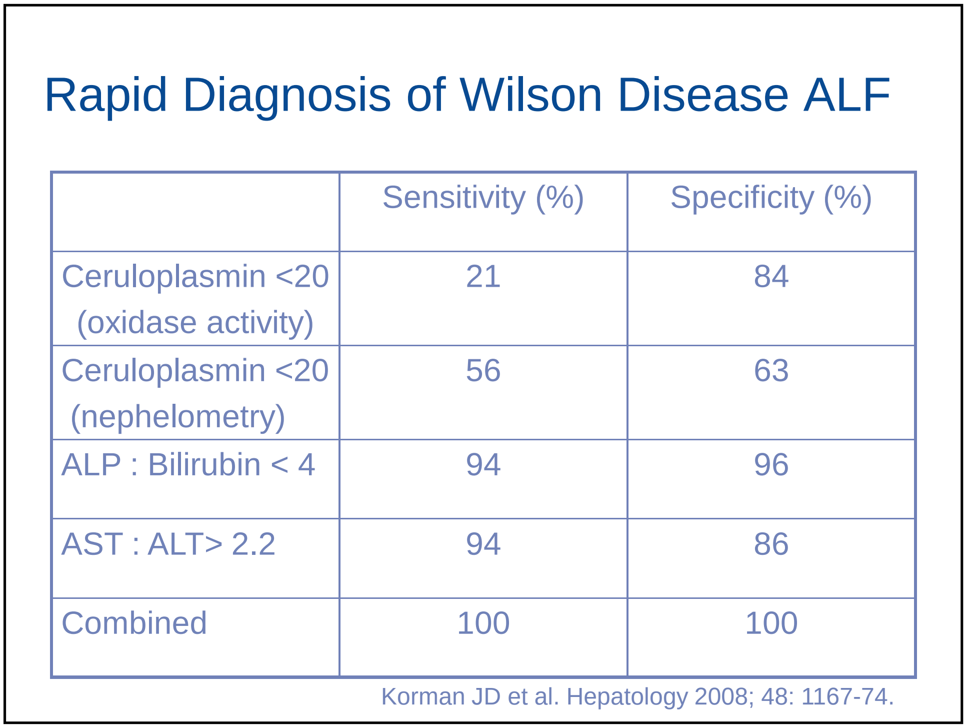
Viral Hepatitis causing ALF

- HBV = 7%, HAV=3%, HCV = 0
- No increased risk of HAV ALF in chronic HCV
- Hep A in US: epidemics related to food contamination
- Hep B most common viral etiology of ALF in US: chemotherapy reactivation
- Parvovirus B19, HDV, HEV, SEN virus, Dengue, HSV, VZV



Wilson Disease

- 5% present with ALF
- Nearly always fatal without transplant
- Clinical characteristics:
  - High bilirubin > 30mg/dl
  - Low Alkaline Phosphatase <20
  - ALP: Bilirubin ratio <2
  - Hemolytic anemia
  - Acute renal failure
  - K-F rings 50% of time
  - Usually cirrhotic



Rapid Diagnosis of Wilson Disease ALF

	Sensitivity (%)	Specificity (%)
Ceruloplasmin <20 (oxidase activity)	21	84
Ceruloplasmin <20 (nephelometry)	56	63
ALP : Bilirubin < 4	94	96
AST : ALT> 2.2	94	86
Combined	100	100

Korman JD et al. Hepatology 2008; 48: 1167-74.

Other Etiologies of ALF

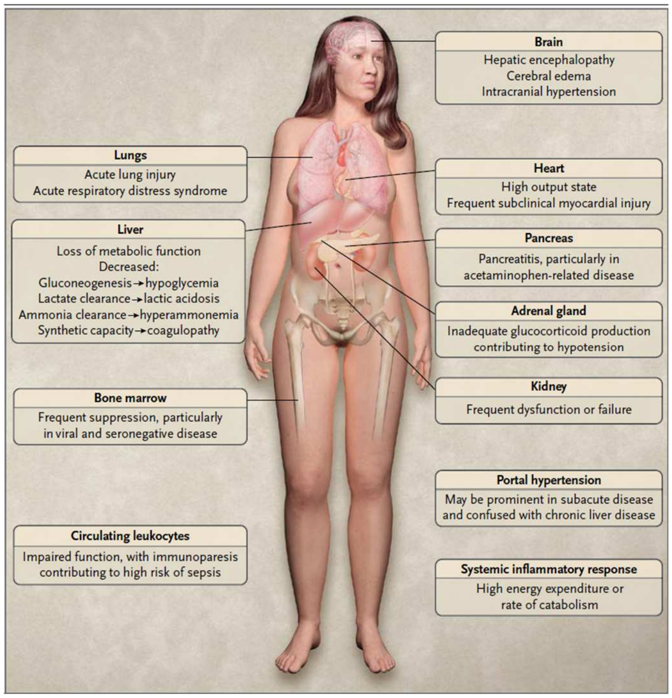
Toxins
    Amanita phalloides
    Organic solvents
    Herbal supplements
Metabolic
    Acute Fatty Liver of Pregnancy
    Reye's syndrome
Vascular
    Shock
    Budd Chiari syndrome
    Venoocclusive disease
    Heat stroke
    Hepatic Artery Thrombosis

Other
    Autoimmune hepatitis
    Tumor infiltration
    Primary graft non-function

Pathogenesis of ALF

Massive hepatocyte necrosis and apoptosis:

- Release of cellular contents
- Components of hepatic failure
- Massive cytokine storm
- Hepatocyte regeneration


Brain
Hepatic encephalopathy
Cerebral edema
Intracranial hypertension
Lungs
Acute lung injury
Acute respiratory distress syndrome
Heart
High output state
Frequent subclinical myocardial injury
Liver
Loss of metabolic function
Decreased:
Gluconeogenesis→hypoglycemia
Lactate clearance→lactic acidosis
Ammonia clearance→hyperammonemia
Synthetic capacity→coagulopathy
Pancreas
Pancreatitis, particularly in acetaminophen-related disease
Adrenal gland
Inadequate glucocorticoid production contributing to hypotension
Kidney
Frequent dysfunction or failure
Bone marrow
Frequent suppression, particularly in viral and seronegative disease
Portal hypertension
May be prominent in subacute disease and confused with chronic liver disease
Circulating leukocytes
Impaired function, with immunoparesis contributing to high risk of sepsis
Systemic inflammatory response
High energy expenditure or rate of catabolism

NEJM 2013; 369: 2526.

Specific ALF Therapies

- N-Acetylcysteine for acetaminophen +/- non-acetaminophen
- Prompt delivery in pregnancy-related ALF (HELLP, AFLP)
- Liver transplantation

- Activated charcoal and high-dose IV penicillin or sibilinin for Amanita mushroom poisoning
- Corticosteroids for autoimmune hepatitis
- Copper chelation, plasmapheresis and antioxidant therapy for Wilson’s disease
- Lamivudine/Entecavir for HBV
- Acyclovir for HSV
- TIPS/surgical decompression for acute Budd-Chiari
- Hemodynamic support for ischemic liver injury

N-Acetylcysteine for ACM ALF

- Should not be withheld even if ACM ingestions >48 hours prior
- Oral is 1st line therapy with mild encephalopathy
- IV for significant encephalopathy, nausea, hypotension
- NAC administration recommended until firm evidence of improved hepatic function (improved encephalopathy, improving INR, declining transaminases)

Intravenous N-Acetylcysteine Improves Transplant Free Survival in Early Stage Non-Acetaminophen Acute Liver Failure

- Overall survival:
  NAC 70% vs. Placebo 66 % (p=0.283)
- Transplant Free Survival:
  NAC 40% vs. Placebo 27% (p=0.43)
- Transplant Rates:
  NAC 32% vs. Placebo 45% (p=0.09)
- Transplant Free Survival Grade I-II Coma:
  NAC 52 % vs. Placebo 30 % (p=0.010)
- Transplant Free Survival Grade III-IV Coma:
  NAC 9% vs. Placebo 22% (p=0.912)
- Side effects minimal, except nausea/vomiting:
  NAC 14% vs. Placebo 4% (p=0.31)

Gastroenterology 2009; 137: 856-864.

Liver Transplantation

- Each year between 3 and 6% of patients listed for transplant are due to ALF
- Overall ~45% ALF patients listed for transplant → 25% receive transplant
- Patients able to be listed Status 1 for 7 days
- ALF post-OLT: 90% survival 1 month, 70% survival 1 year
- Most diseases do not recur: ACM with repeated overdose, post-OLT AIH

Nonspecific therapies for ALF

Therapeutic Hypothermia (TH):

Grade III or IV encephalopathy

TH 32-35° in 97 ALF patients,1125 controls

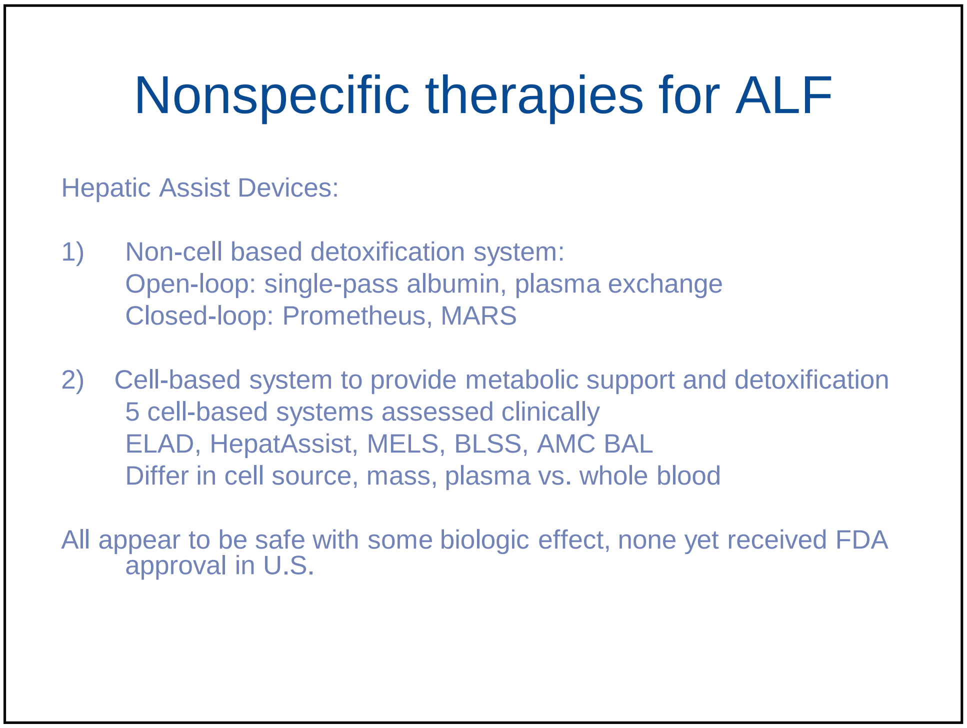
ICP was measured in 39.2% TH and 22% controls

TH was not associated with increased bleeding or infections

Survival improved in TH in APAP < 25 years old (OR: 2.75)

TH did not affect 21-day overall and transplant free survival

Liver Transplantation 2015; 21: 4-12.



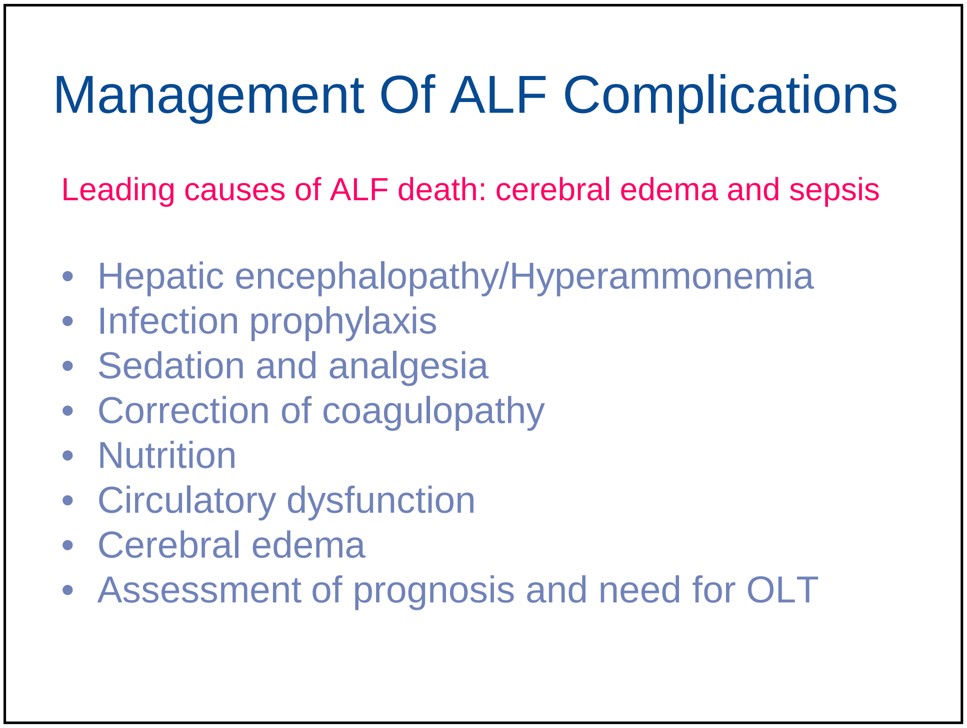
Nonspecific therapies for ALF

Hepatic Assist Devices:

1) Non-cell based detoxification system:
   Open-loop: single-pass albumin, plasma exchange
   Closed-loop: Prometheus, MARS

2) Cell-based system to provide metabolic support and detoxification
   5 cell-based systems assessed clinically
   ELAD, HepatAssist, MELS, BLSS, AMC BAL
   Differ in cell source, mass, plasma vs. whole blood

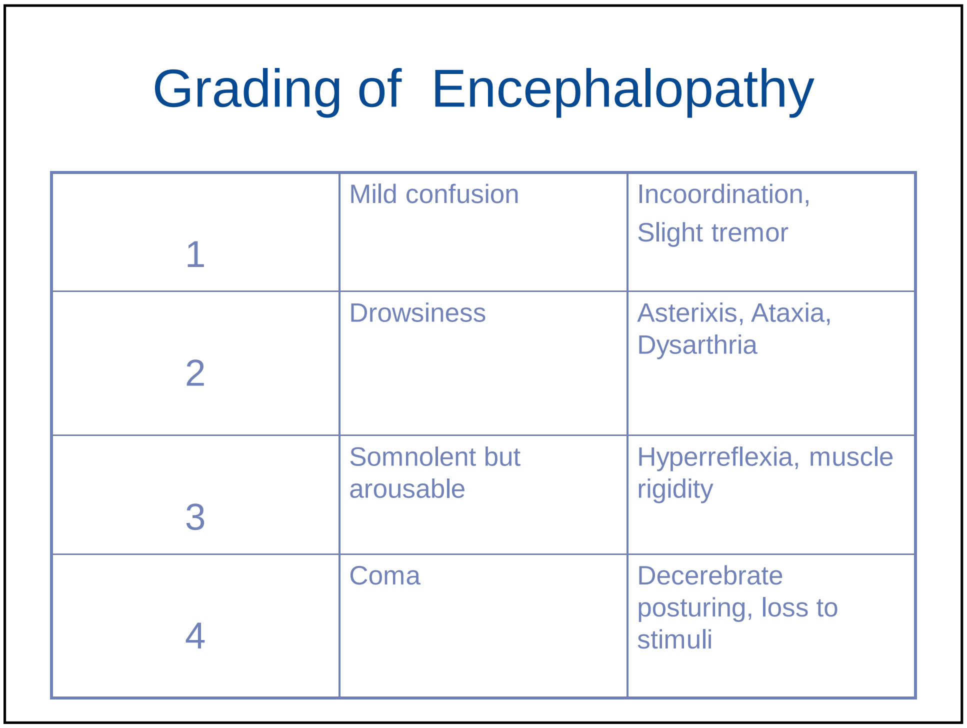
All appear to be safe with some biologic effect, none yet received FDA approval in U.S.



Management Of ALF Complications

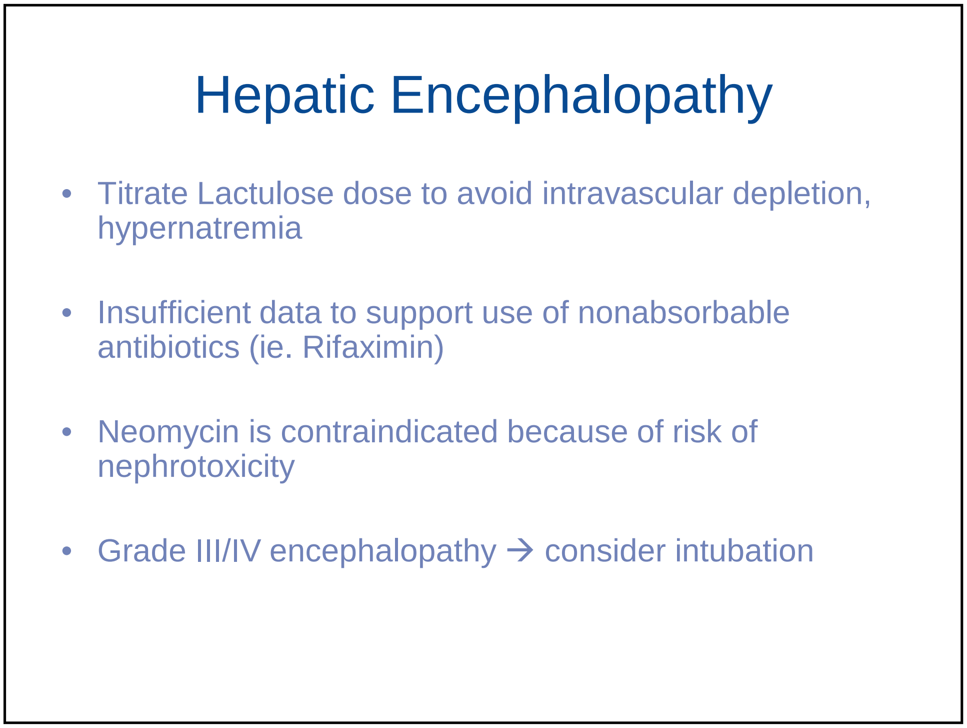
Leading causes of ALF death: cerebral edema and sepsis

- Hepatic encephalopathy/Hyperammonemia
- Infection prophylaxis
- Sedation and analgesia
- Correction of coagulopathy
- Nutrition
- Circulatory dysfunction
- Cerebral edema
- Assessment of prognosis and need for OLT



Grading of Encephalopathy

1	Mild confusion	Incoordination, Slight tremor
2	Drowsiness	Asterixis, Ataxia, Dysarthria
3	Somnolent but arousable	Hyperreflexia, muscle rigidity
4	Coma	Decerebrate posturing, loss to stimuli



Hepatic Encephalopathy

- Titrate Lactulose dose to avoid intravascular depletion, hypernatremia
- Insufficient data to support use of nonabsorbable antibiotics (ie. Rifaximin)
- Neomycin is contraindicated because of risk of nephrotoxicity
- Grade III/IV encephalopathy → consider intubation

Infection Prophylaxis

- Lung > urinary tract and blood
- Fungal infections in up to 1/3 ALF patients
- Insufficient data to support routine antibiotic prophylaxis in all ALF patients, particularly with early encephalopathy
- Daily surveillance blood cultures and CXR recommended → ALF pts may not exhibit standard infectious signs
- Empiric antibiotics recommended if: surveillance culture with significant isolate, progression or advanced (stage III/IV) encephalopathy, refractory hypotension or presence of SIRS

Sedation and Analgesia

- Psychomotor agitation and pain can increase intracranial pressure
- Propofol and benzodiazepines, most popular, may exacerbate encephalopathy
- Recovery from Propofol short to allow quicker neurologic examination
- Propofol decreases cerebral blood flow which lowers intracranial pressure
- Morphine and Demerol not recommended due to active metabolites accumulating

Correction of coagulopathy

- Spontaneous, clinically significant bleeding is uncommon in ALF patients (<10%)
- Vitamin K 10mg SC x 3 days
- Prophylactic FFP not recommended
- Cryoprecipitate recommended in hypofibrinogenemia (<100 mg/dL)
- Recombinant factor VIIa before high-risk bleeding procedures (biopsy, ICP monitor placement)
- IV PPI or IV H-2 receptor antagonists shown to reduce risk of GI bleeding in ALF patients

Nutrition

- ALF is catabolic state (60g/day of protein) - Do Not Protein Restrict
- Enteral nutrition whenever possible
- Higher caloric density feeds may avoid excessive free water → cerebral edema
- Hyperglycemia may exacerbate intracranial hypertension (blood glucose < 150 mg/dl)

Circulatory Dysfunction

- Vasopressors recommended for SBP <90 mmHg, MAP <65 or to achieve cerebral perfusion pressure 50-80mm Hg (MAP – ICP)
- Norepinephrine shown to generate consistent and predictable increase in cerebral perfusion in head trauma patients
- Relative adrenal insufficiency occurs frequently in ALF → hydrocortisone with refractory hypotension

Encephalopathy and Cerebral Edema

Grade	Incidence
1	Rare
2	Rare
3	25%
4	75%

Admission Ammonia and Cerebral Edema

- Ammonia < 75 µM rarely develops ICH
- Ammonia > 100 µM independent risk factor for high grade encephalopathy
- Ammonia > 200 µM predicts ICH

Hepatology 2007; 46: 1844-1852.

Prevent Cerebral Edema

- Cerebral edema most likely in most acute ALF presentations (ACM)
- Head CT and intubation for stage III/IV encephalopathy
- No randomized studies to guide indications for ICP monitor placement
- Most centers place ICP monitors in stage III/IV encephalopathy in patients listed for OLT
- Bleeding complications with ICP monitor placement 10-20%

- Quiet environment with limited stimulation
- Head of bed elevated to 30 degrees
- Mild hypothermia (ie. CVVH) should not be treated
- Corticosteroids not useful in cytotoxic cerebral edema
- Severe (>40mm Hg) sustained intracranial hypertesion refractory to medical therapy → brainstem herniation and poor neurologic recovery post-OLT
- No data to support empiric use of treatments to reduce ICP

Treat Cerebral Edema

- Involve neurosurgery early
- Hypertonic saline boluses every 2-3 hours (aim serum Na+ 145-155)
- Aim for hyperventilation induced hypocapnia, pCO2~ 30mmHg
- When ICP >= 25mm Hg for > 10 minutes, first-line Mannitol
- Barbiturate coma (pentobarbital or thiopental) in mannitol refractory cerebral edema
- No RCT data on therapeutic hypothermia

Assessment of Prognosis and Need for Transplant

- Etiology an important outcome determinant
- No prognostic criteria adequately sensitive or specific
- King's College Criteria: Sensitivity 61%, Specificity 86%
- MELD > 32: Sensitivity 77%, Specificity 72%
- Factor VIII/V, arterial phosphate, arterial lactate, arterial ammonia, serum apoptosis markers), APACHE II score, AFP

Outcome in ALF

90% have definitive outcome at 3 weeks

Transplant-free survival	45%
Liver Transplantation	25%
Death without transplantation	30%

Etiology and Outcome in ALF

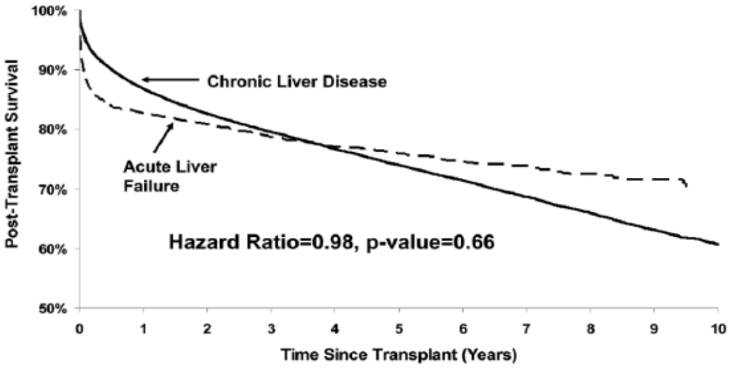
	Acetaminophen	Drugs	Indeterminate	Hep A	Hep B	Others
Transplant Free Survival	65%	29%	25%	58%	25%	34%
Transplant	9%	41%	43%	29%	47%	33%
Death Without Transplant	26%	31%	32%	13%	28%	33%

Liver Transplantation

Why do only 25% receive liver graft?

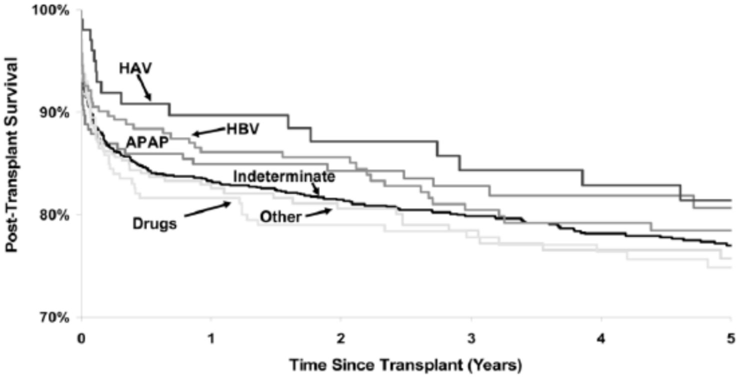
- Rapidly fatal disease with organ shortage
- No hepatic assist devices FDA approved, unable to bridge to transplant
- Prognosis difficult to assess
- Late presentation can preclude listing
- Some patients not transplant candidates

ALF Post Transplantation



Hepatology 2008; 47: 1401-1415

ALF Post Transplantation



Hepatology 2008; 47: 1401-1415

SUMMARY

- Coagulopathy, encephalopathy onset < 26 weeks
- Acetaminophen + Drug > 50% etiology of ALF in U.S.
- Good prognosis: Acetaminophen, HAV, Shock
- Poor prognosis: Drug, Indeterminate, HBV, Wilson's
- Liver transplantation has improved ALF survival
- Overall 45% patients survive without transplant
- IV NAC proven benefit in all etiologies of ALF
- Worse admission coma grade portends worse prognosis
- Limited effective clinical prognostic markers in ALF, etiology often most helpful

SELECT REFERENCES

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Flamm SL et al. American Gastroenterological Association Institute Guidelines for the Diagnosis and Management of Acute Liver Failure. Gastroenterology 2017; 152: 644-647.

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Lee WM et al. IV N-acetylcysteine improves transplant-free survival in early-stage non-acetaminophen acute liver failure. Gastroenterology 2009; 137: 856-864.

Nguyen NTT el al. Acute Liver Failure. Current Opinion in Organ Transplantation 2011; 16: 289-296.

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Question #1

19 year old male presents to PCP with 2 weeks post-prandial nausea and abdominal pain. His labs are noted below. Based on this presentation your working diagnoses would include:

6/3: TB: 10.9, DB: 5.9, AST: 2155, ALT: 2863
6/6: TB: 14.8, DB: 8.8, AST: 3225, ALT: 2873, INR 2.3

Question #1

a) Acetaminophen, Viral, Wilson’s Disease

b) Drug, Viral, Alcoholic Hepatitis

c) Amanita phalloides (mushroom), Wilson’s Disease, Viral

d) Shock liver, Autoimmune Hepatitis, Acetaminophen

e) Viral, Wilson’s Disease, Autoimmune Hepatitis

Answer #1

a) Acetaminophen, Viral, Wilson’s Disease

b) Drug, Viral, Alcoholic Hepatitis

c) Amanita phalloides, Wilson’s Disease, Viral

d) Shock liver, Autoimmune Hepatitis, Acetaminophen

e) Viral, Wilson’s Disease, Autoimmune Hepatitis

Question #2

Patient sent to ER. TB: 20.0, INR: 3.2
Tylenol level negative, Negative Hep A/B/C
RUQ U/S with biliary wall thickening, normal Doppler flow
No medications, OTC supplements, herbals, mushrooms
No IVDU, sexual exposures, travel, rare etoh

Over course of ER evaluation he becomes sleepy and slightly confused

Your next steps in his management should include:

Question #2

a) Admit to ICU, Intubate, FFP to keep INR <1.5
b) Serum/urine tox screen, IV NAC, Hypertonic saline
c) IV NAC, Head CT, Refer to transplant center
d) Slit-lamp exam, IV steroids, Lactulose
e) Plasmapheresis, D5W, Refer to transplant center

Answer #2

a) Admit to ICU, Intubate, FFP to keep INR <1.5
b) Serum/urine tox screen, IV NAC, Hypertonic saline
c) IV NAC, Head CT, Refer to transplant center
d) Slit-lamp exam, PO NAC, Lactulose
e) Plasmapheresis, D5W, Refer to transplant center

Question #3

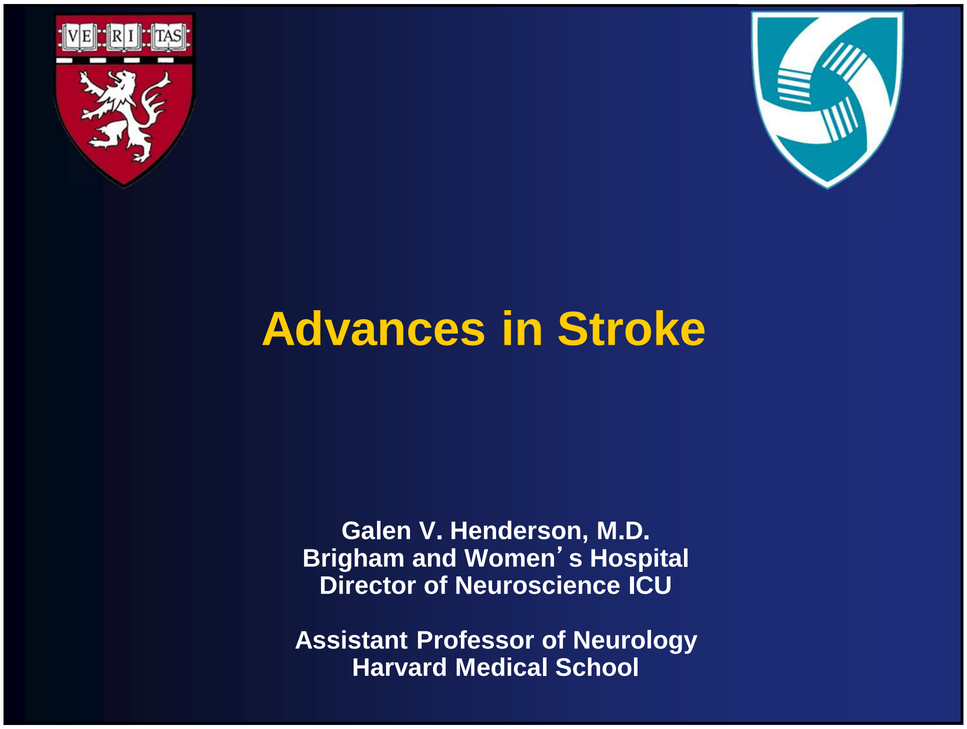
If this case were determined to be an unintentional Acetaminophen overdose, which of the following statements is true:

Question #3

a) Due to chronic acetaminophen toxicity, patient is unlikely to survive without liver transplant
b) Patient would not meet criteria for transplant listing as he is likely addicted to narcotics
c) Men far more likely to take unintentional acetaminophen overdoses than women
d) Patient's chance of transplant-free survival is about 65%
e) N-acetylcysteine is not effective in unintentional acetaminophen overdose due to the long time between ingestion and presentation

Answer #3

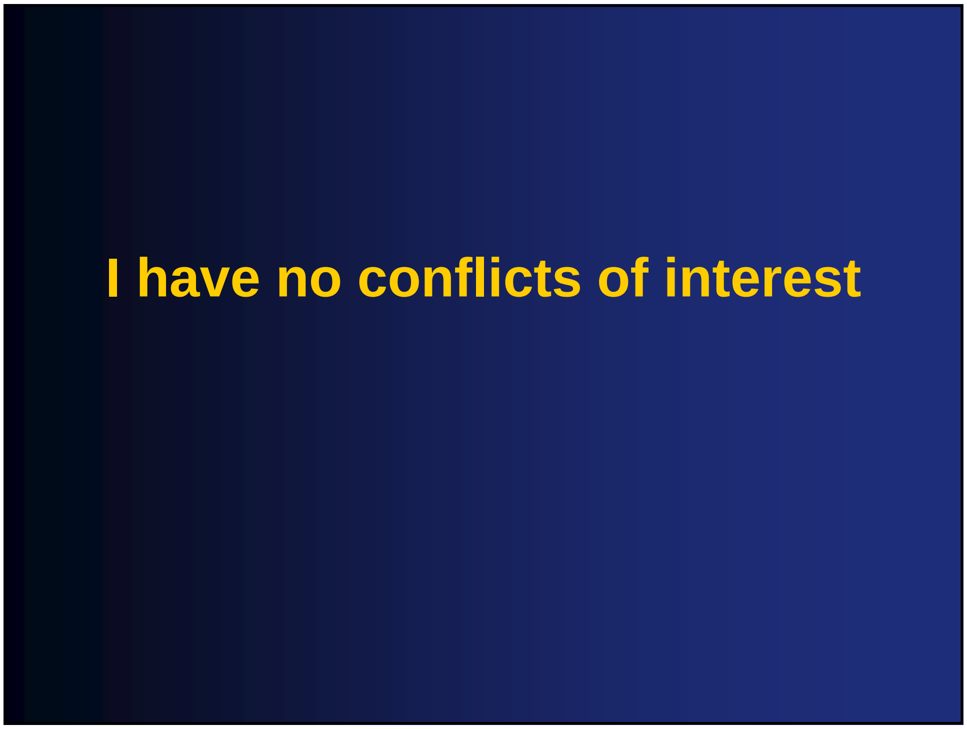
a) Due to chronic acetaminophen toxicity, patient is unlikely to survive without transplant
b) Patient would not meet criteria for transplant listing as he is likely addicted to narcotics
c) Men far more likely to take unintentional acetaminophen overdoses than women
d) Patient's chance of transplant-free survival is about 65%
e) N-acetylcysteine is not effective in unintentional acetaminophen overdose due to the longer time between ingestion and presentation



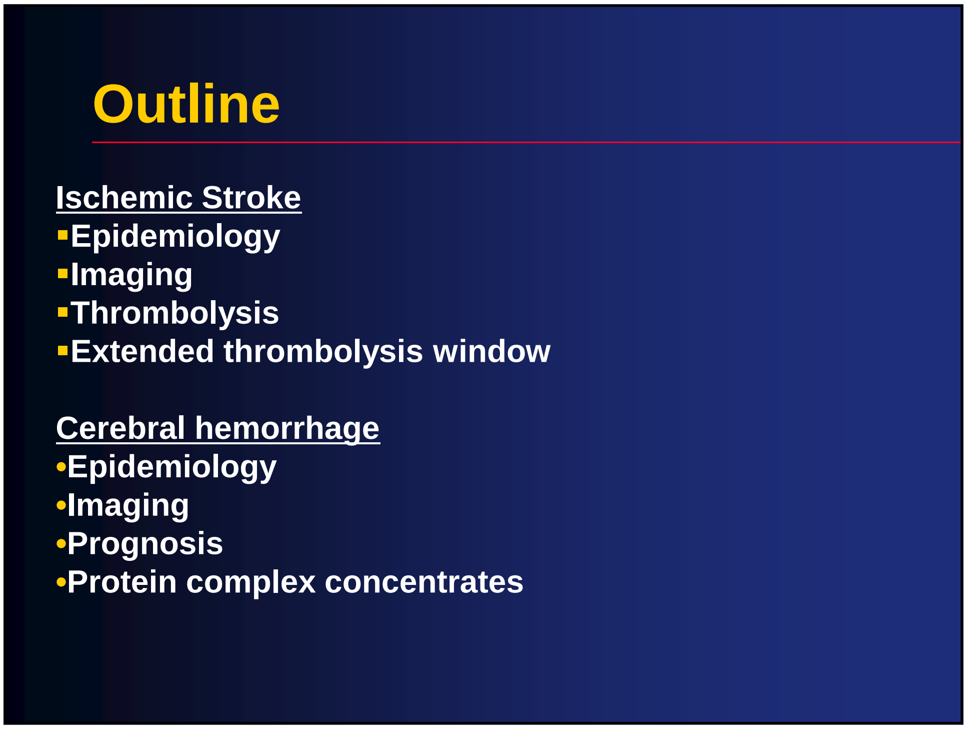
Advances in Stroke

Galen V. Henderson, M.D.
Brigham and Women's Hospital
Director of Neuroscience ICU

Assistant Professor of Neurology
Harvard Medical School



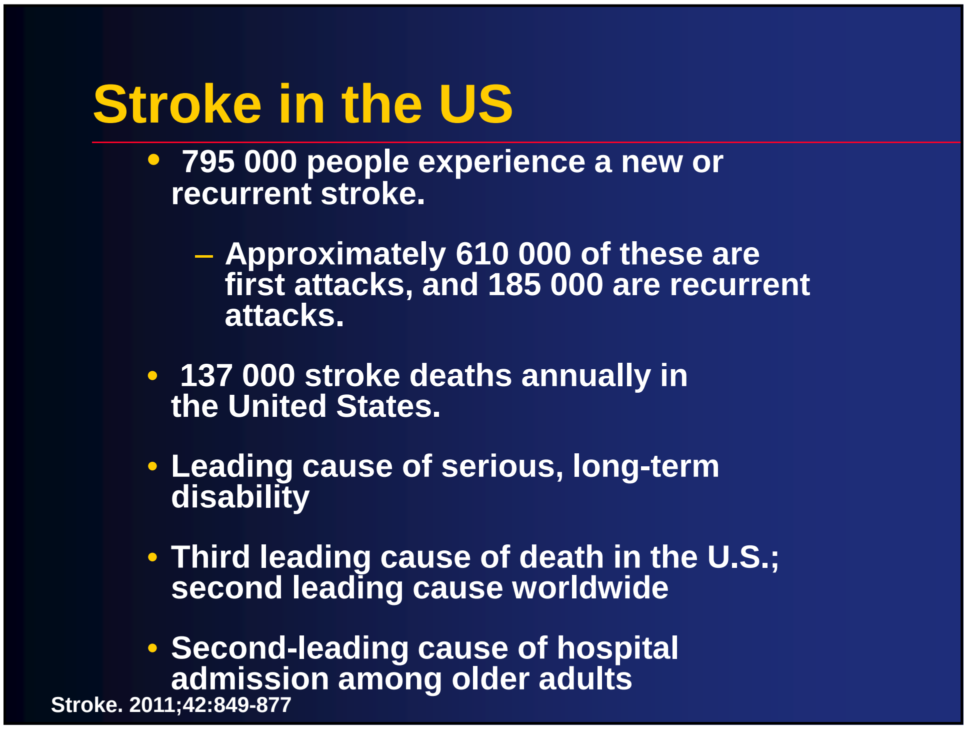
I have no conflicts of interest



Outline

Ischemic Stroke
- Epidemiology
- Imaging
- Thrombolysis
- Extended thrombolysis window

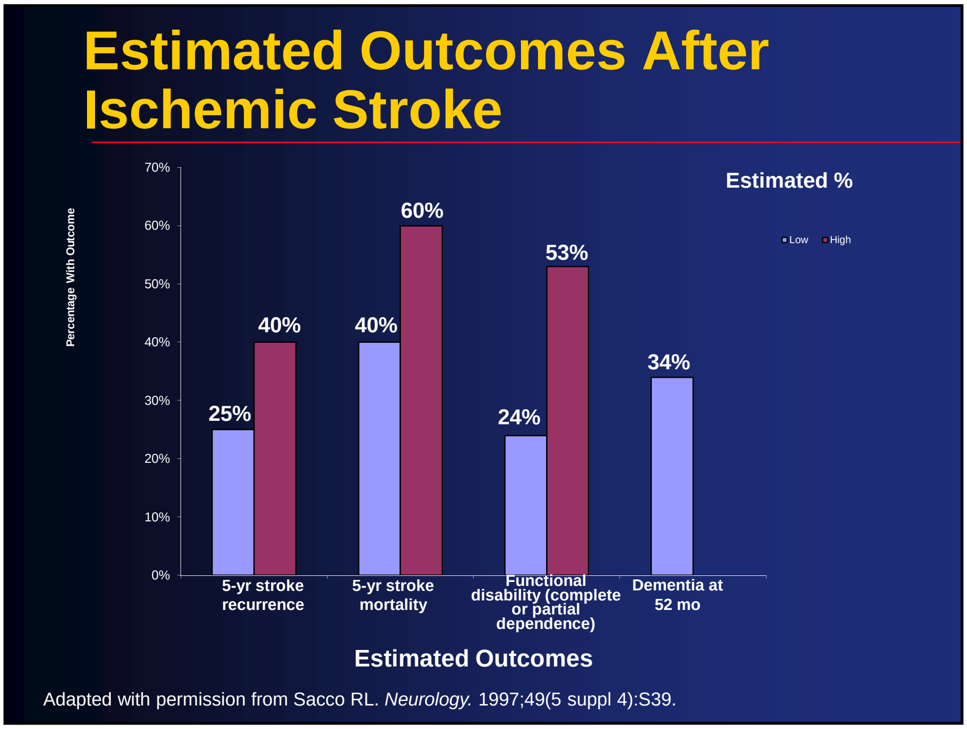
Cerebral hemorrhage
- Epidemiology
- Imaging
- Prognosis
- Protein complex concentrates



Stroke in the US

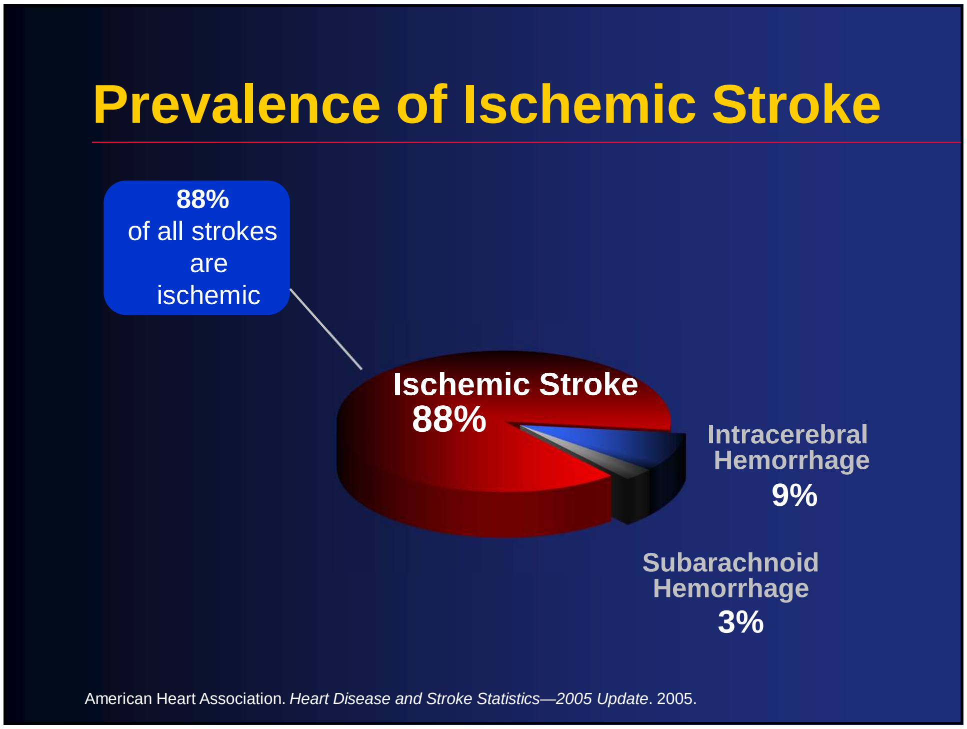
- 795 000 people experience a new or recurrent stroke.
  - Approximately 610 000 of these are first attacks, and 185 000 are recurrent attacks.
- 137 000 stroke deaths annually in the United States.
- Leading cause of serious, long-term disability
- Third leading cause of death in the U.S.; second leading cause worldwide
- Second-leading cause of hospital admission among older adults

Stroke. 2011;42:849-877



Estimated Outcomes After Ischemic Stroke

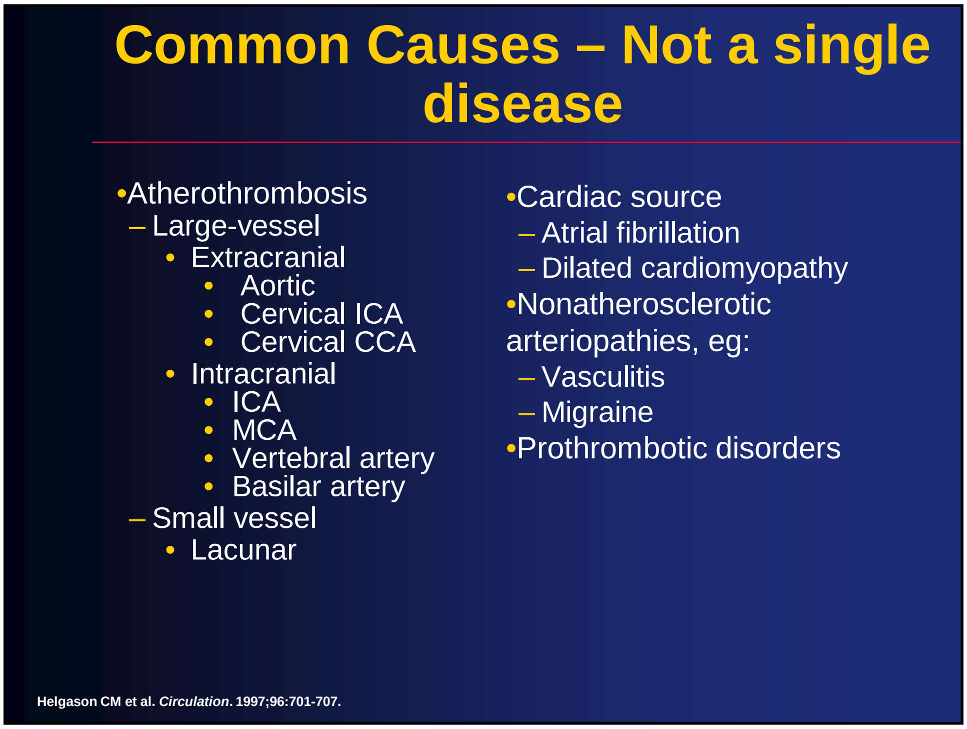
Adapted with permission from Sacco RL. *Neurology.* 1997;49(5 suppl 4):S39.



Prevalence of Ischemic Stroke

88%
of all strokes
are
ischemic

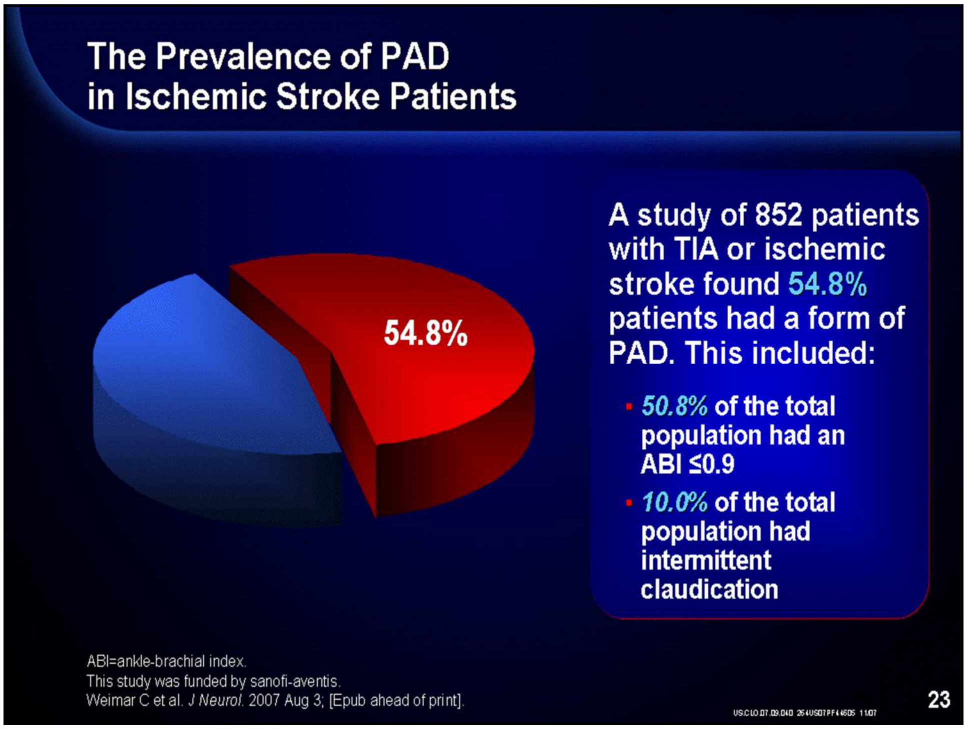
American Heart Association. *Heart Disease and Stroke Statistics—2005 Update*. 2005.



Common Causes – Not a single disease

- Atherothrombosis
  - Large-vessel
    - Extracranial
      - Aortic
      - Cervical ICA
      - Cervical CCA
    - Intracranial
      - ICA
      - MCA
      - Vertebral artery
      - Basilar artery
  - Small vessel
    - Lacunar
- Cardiac source
  - Atrial fibrillation
  - Dilated cardiomyopathy
- Nonatherosclerotic arteriopathies, eg:
  - Vasculitis
  - Migraine
- Prothrombotic disorders

Helgason CM et al. *Circulation*. 1997;96:701-707.



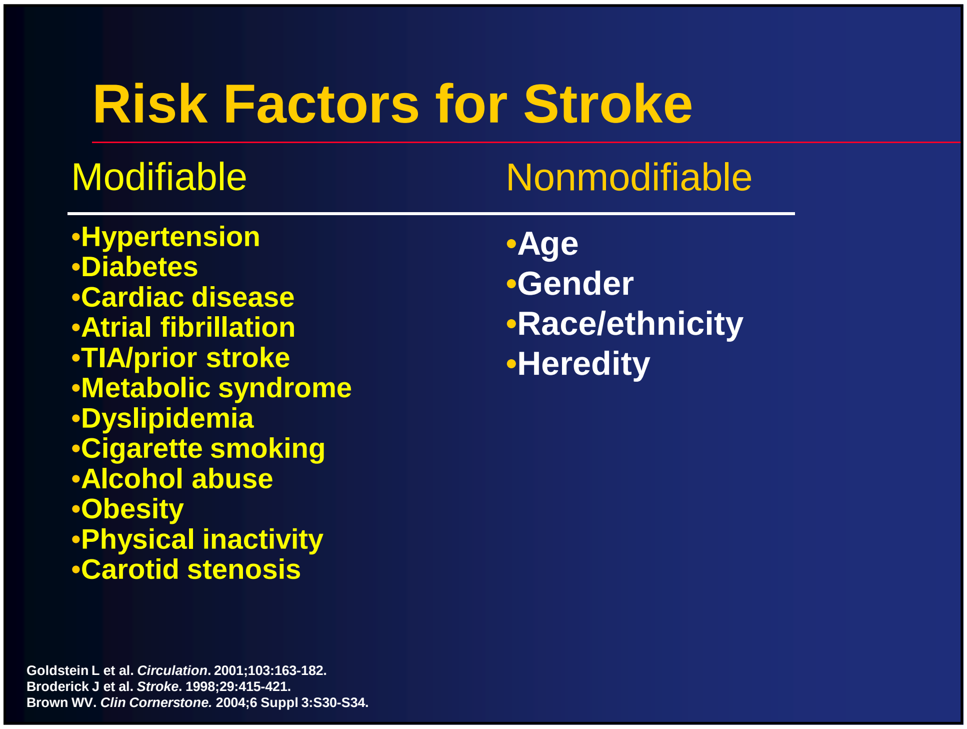
The Prevalence of PAD in Ischemic Stroke Patients

A study of 852 patients with TIA or ischemic stroke found 54.8% patients had a form of PAD. This included:

- *50.8%* of the total population had an ABI ≤0.9
- *10.0%* of the total population had intermittent claudication

ABI=ankle-brachial index.
This study was funded by sanofi-aventis.
Weimar C et al. *J Neurol*. 2007 Aug 3; [Epub ahead of print].

US.CLO.07.09.040 264US07PF44505 11/07



Risk Factors for Stroke

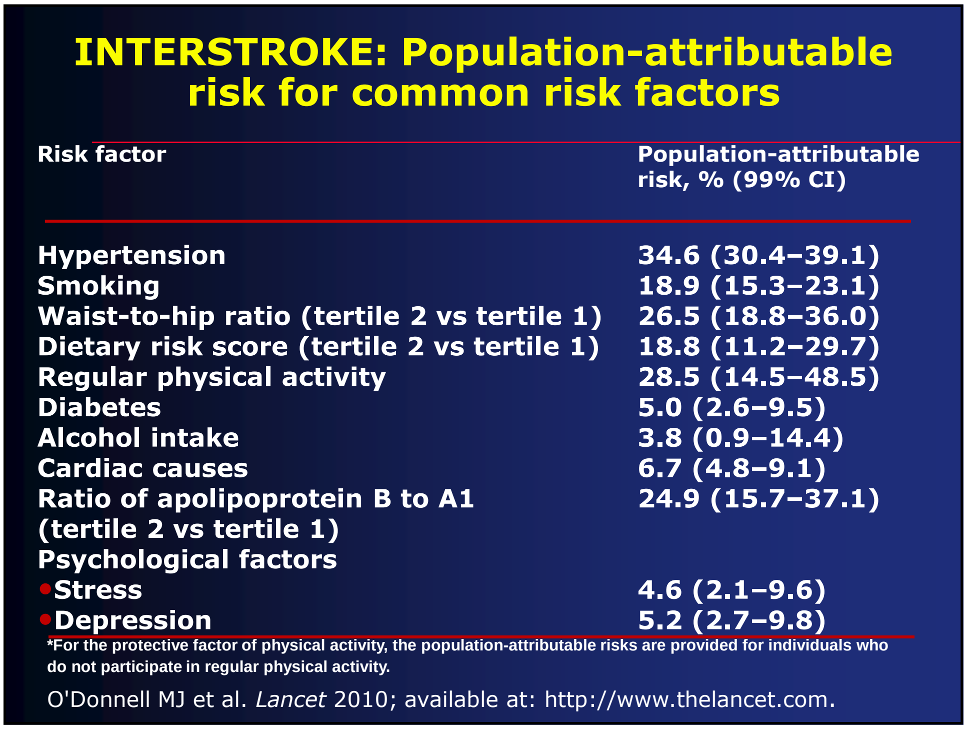
Modifiable

- Hypertension
- Diabetes
- Cardiac disease
- Atrial fibrillation
- TIA/prior stroke
- Metabolic syndrome
- Dyslipidemia
- Cigarette smoking
- Alcohol abuse
- Obesity
- Physical inactivity
- Carotid stenosis

Nonmodifiable

- Age
- Gender
- Race/ethnicity
- Heredity

Goldstein L et al. *Circulation*. 2001;103:163-182.
Broderick J et al. *Stroke*. 1998;29:415-421.
Brown WV. *Clin Cornerstone*. 2004;6 Suppl 3:S30-S34.

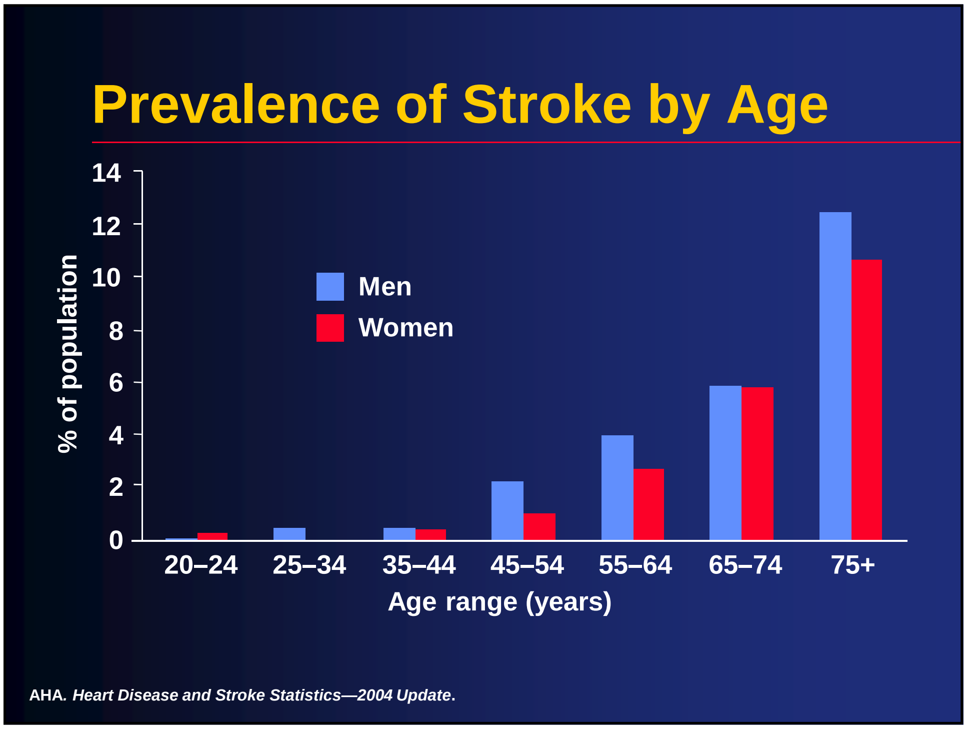


INTERSTROKE: Population-attributable risk for common risk factors

Risk factor	Population-attributable risk, % (99% CI)
Hypertension	34.6 (30.4–39.1)
Smoking	18.9 (15.3–23.1)
Waist-to-hip ratio (tertile 2 vs tertile 1)	26.5 (18.8–36.0)
Dietary risk score (tertile 2 vs tertile 1)	18.8 (11.2–29.7)
Regular physical activity	28.5 (14.5–48.5)
Diabetes	5.0 (2.6–9.5)
Alcohol intake	3.8 (0.9–14.4)
Cardiac causes	6.7 (4.8–9.1)
Ratio of apolipoprotein B to A1 (tertile 2 vs tertile 1)	24.9 (15.7–37.1)
Psychological factors	
• Stress	4.6 (2.1–9.6)
• Depression	5.2 (2.7–9.8)

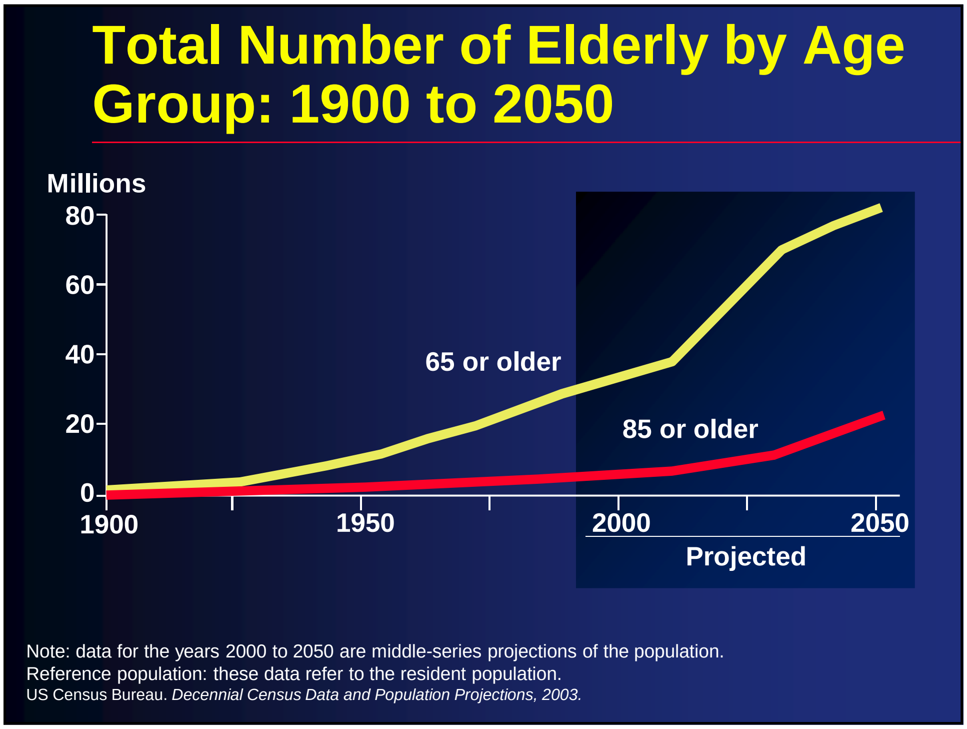
*For the protective factor of physical activity, the population-attributable risks are provided for individuals who do not participate in regular physical activity.

O'Donnell MJ et al. *Lancet* 2010; available at: http://www.thelancet.com.



Prevalence of Stroke by Age

AHA. *Heart Disease and Stroke Statistics—2004 Update*.



Total Number of Elderly by Age Group: 1900 to 2050

Note: data for the years 2000 to 2050 are middle-series projections of the population.
Reference population: these data refer to the resident population.
US Census Bureau. *Decennial Census Data and Population Projections, 2003.*

Transient Ischemic Attacks (TIAs)

Historic Definition

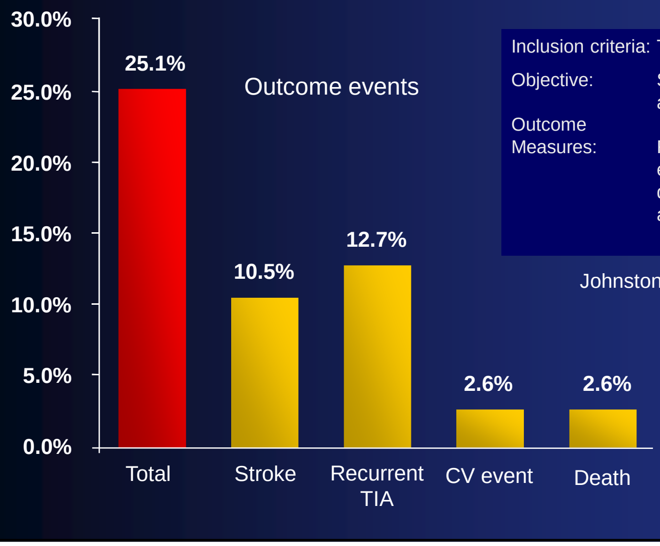
Temporary focal brain or retinal deficits caused by vascular disease that *resolve within 24 hours*

New Definition of TIA

TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting *less than one hour*, and *without evidence of acute infarction*

N Engl J Med, Vol. 337, Nov 21, 2002, 1713-1717.
Stroke, Vol 37, 2006, 577-617.
Stroke. 2009;40:2276.

Short-term Prognosis after Emergency Department Diagnosis of TIA



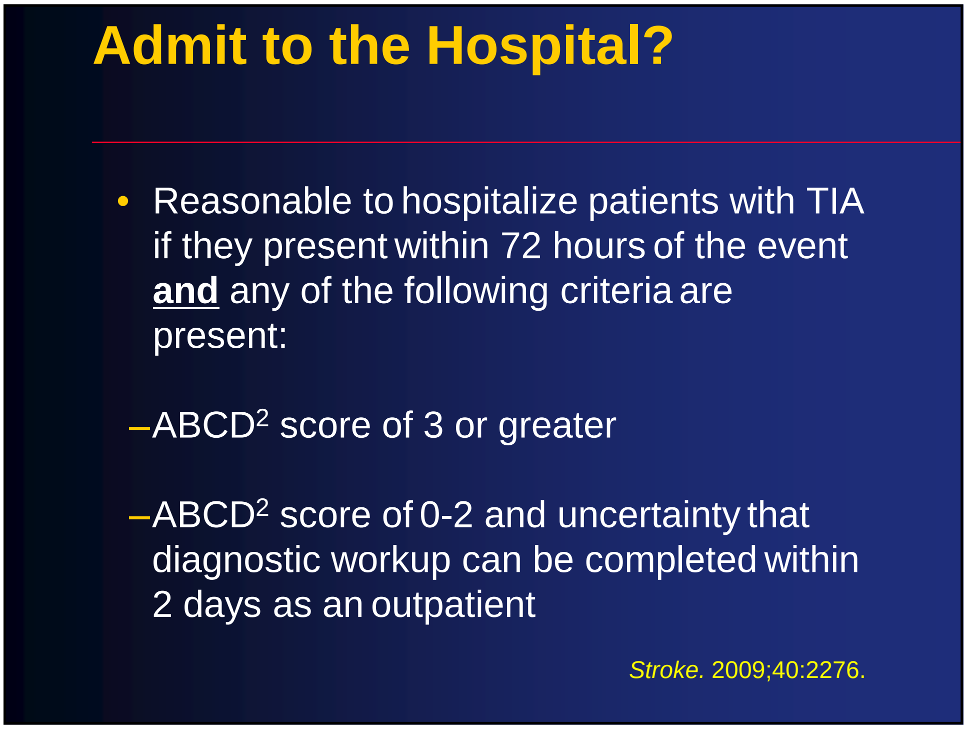
Inclusion criteria:	TIA by ED physicians
Objective:	Short-term risk of stroke after ED diagnosis
Outcome Measures:	Risk of stroke and other events during the 90 days after index TIA

Johnston SC. et al. JAMA 2000; 284: 2901-2906

ABCD^2 of TIA

- **Patients with TIA score points for each of the following factors:**
  - Age 60 years (1 point)
  - Blood pressure 140/90 mm Hg on first evaluation (1 point)
  - Clinical symptoms of focal weakness with the spell (2 points) or speech impairment without weakness (1point)
  - Duration 60 minutes (2 points) or 10 to 59 minutes (1 point)
  - Diabetes (1 point).
  - 2-day risk of stroke:
    - 0% for scores of 0 -1
    - 1.3% for 2 -3
    - 3, 4.1% for 4-5
    - 8.1% for 6-7

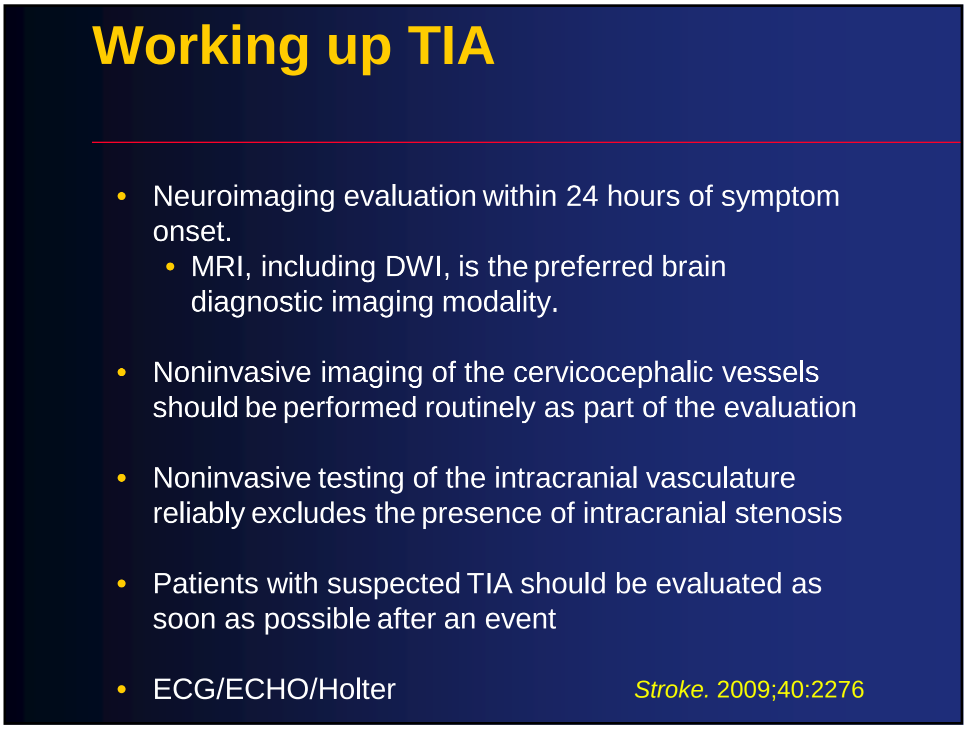
Stroke. 2009;40:2276.



Admit to the Hospital?

- Reasonable to hospitalize patients with TIA if they present within 72 hours of the event **and** any of the following criteria are present:
  - ABCD^2 score of 3 or greater
  - ABCD^2 score of 0-2 and uncertainty that diagnostic workup can be completed within 2 days as an outpatient

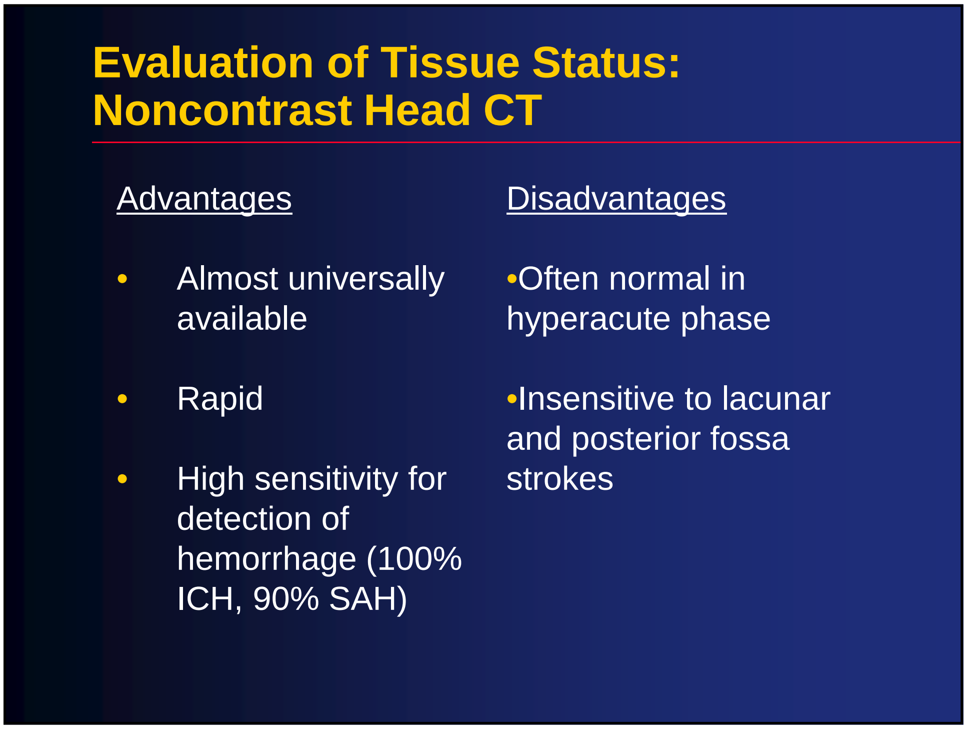
Stroke. 2009;40:2276.



Working up TIA

- Neuroimaging evaluation within 24 hours of symptom onset.
  - MRI, including DWI, is the preferred brain diagnostic imaging modality.
- Noninvasive imaging of the cervicocephalic vessels should be performed routinely as part of the evaluation
- Noninvasive testing of the intracranial vasculature reliably excludes the presence of intracranial stenosis
- Patients with suspected TIA should be evaluated as soon as possible after an event
- ECG/ECHO/Holter

Stroke. 2009;40:2276



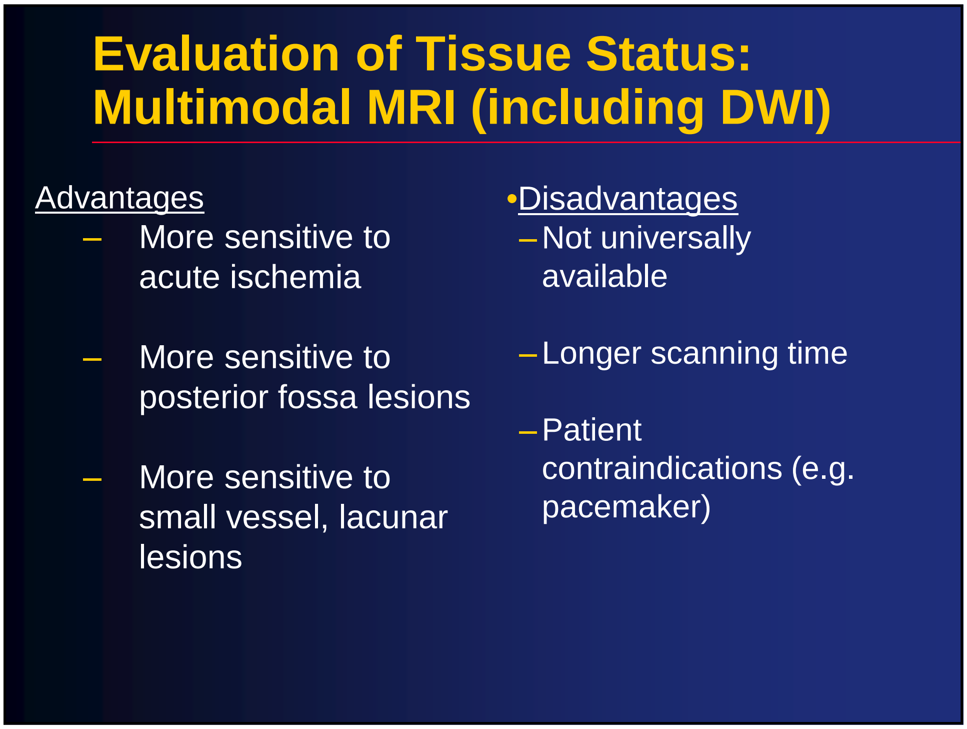
Evaluation of Tissue Status: Noncontrast Head CT

Advantages

- Almost universally available
- Rapid
- High sensitivity for detection of hemorrhage (100% ICH, 90% SAH)

Disadvantages

- Often normal in hyperacute phase
- Insensitive to lacunar and posterior fossa strokes



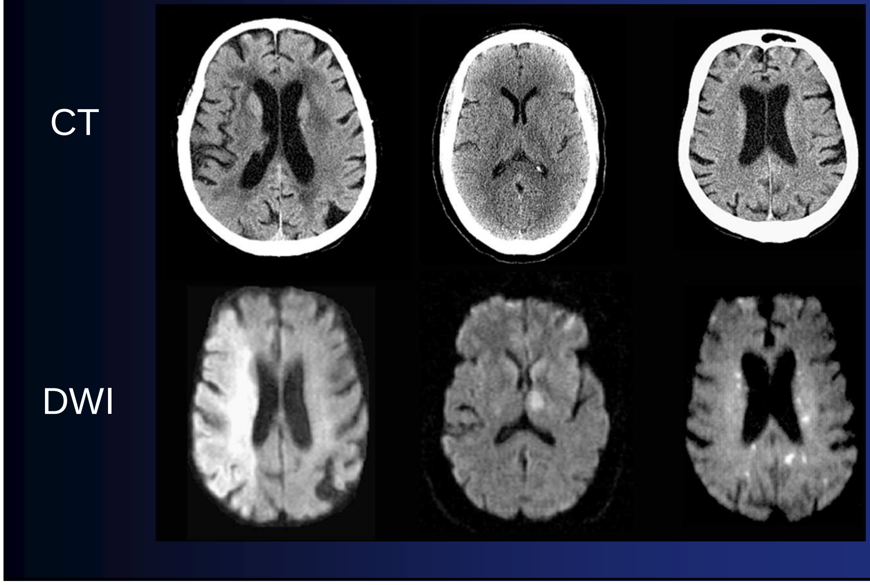
Evaluation of Tissue Status: Multimodal MRI (including DWI)

Advantages

- More sensitive to acute ischemia
- More sensitive to posterior fossa lesions
- More sensitive to small vessel, lacunar lesions

- Disadvantages
  - Not universally available
  - Longer scanning time
  - Patient contraindications (e.g. pacemaker)

MRI - Tissue Status: Ischemia



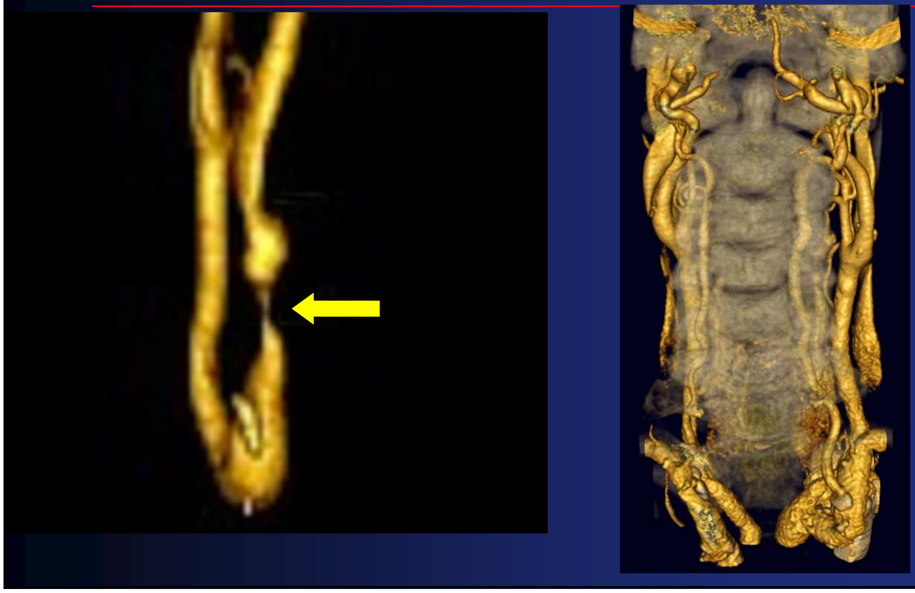
Evaluation of Vessel Status

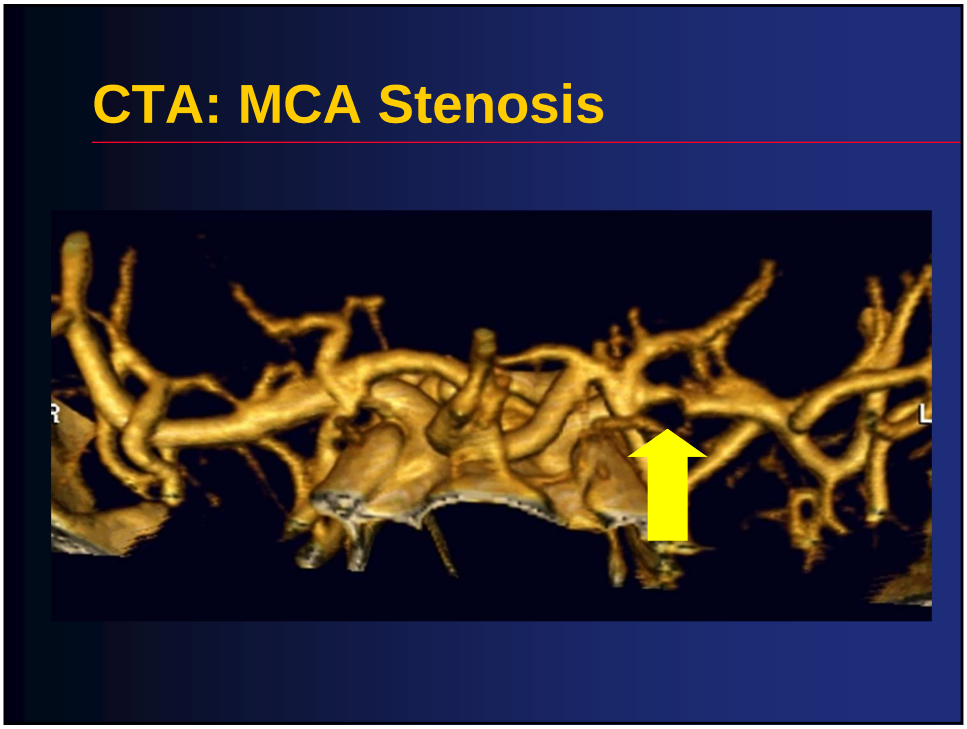
1. CT Angiography
2. MR Angiography
3. Ultrasound Techniques
4. Catheter Angiography

CT Angiography

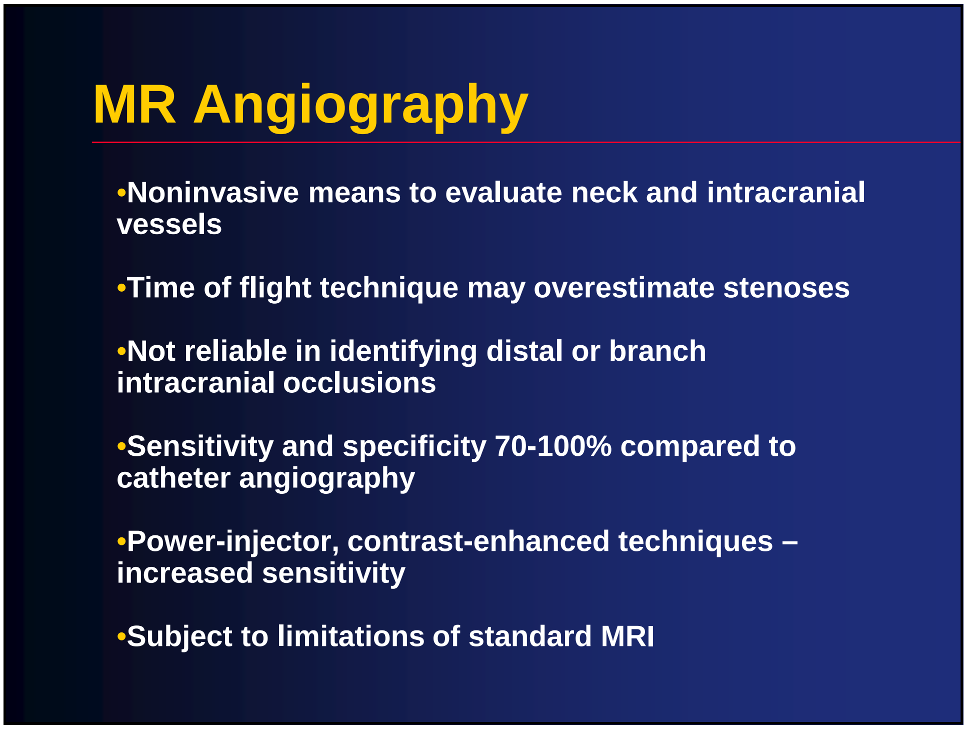
- Requires injection of intravenous contrast agent
- New generation helical scanners allow rapid evaluation of aortic arch, neck, and intracranial vessels with 1 injection
- 80-100% accuracy compared with catheter angiography
- Disadvantages: iodinated contrast agent, radiation exposure

CTA: Carotid Stenosis



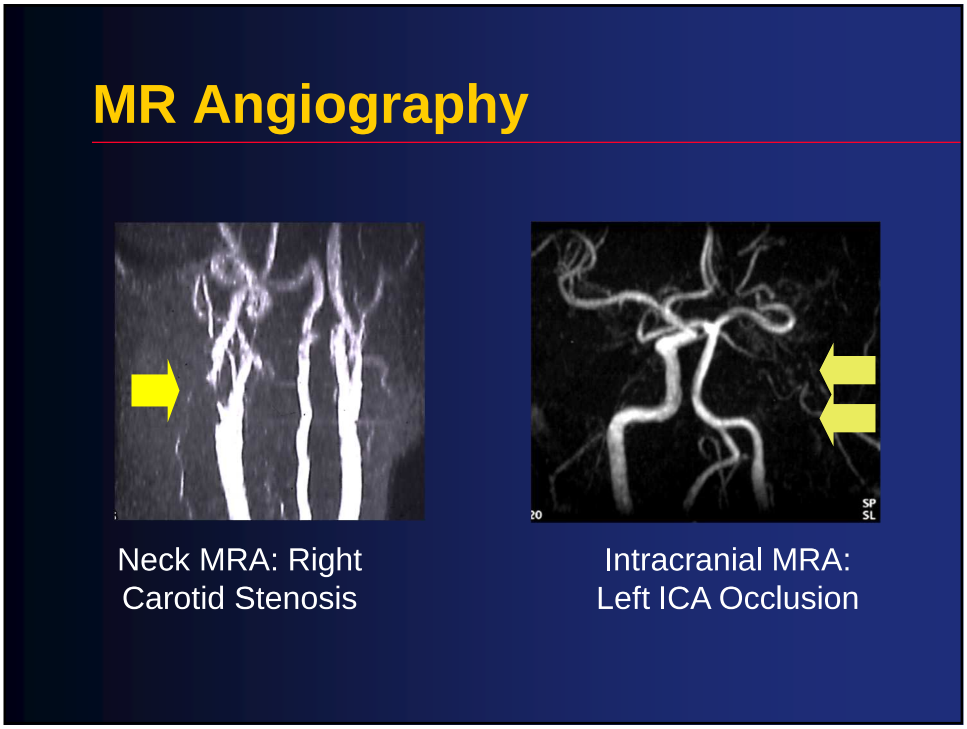


CTA: MCA Stenosis



MR Angiography

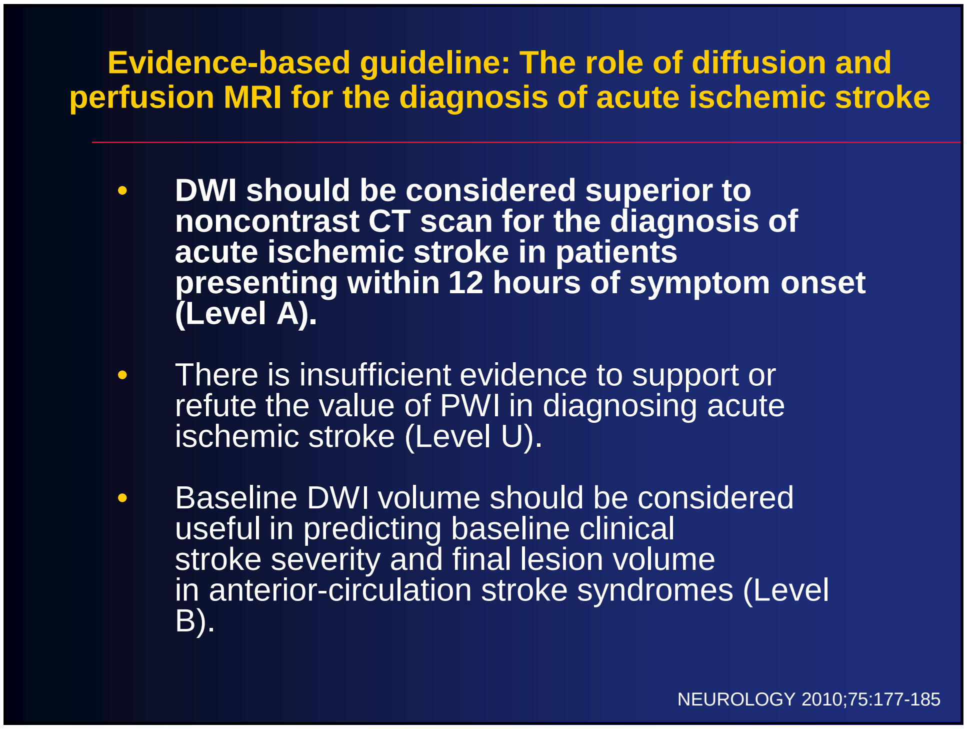
- Noninvasive means to evaluate neck and intracranial vessels
- Time of flight technique may overestimate stenoses
- Not reliable in identifying distal or branch intracranial occlusions
- Sensitivity and specificity 70-100% compared to catheter angiography
- Power-injector, contrast-enhanced techniques – increased sensitivity
- Subject to limitations of standard MRI



MR Angiography

Neck MRA: Right Carotid Stenosis

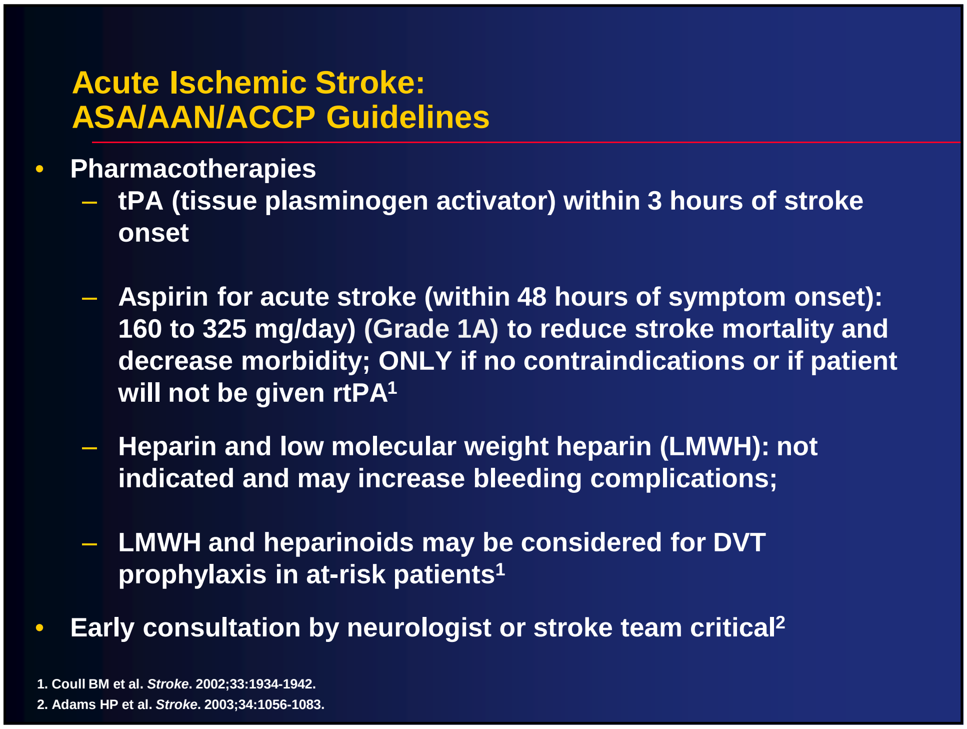
Intracranial MRA: Left ICA Occlusion



Evidence-based guideline: The role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke

- **DWI should be considered superior to noncontrast CT scan for the diagnosis of acute ischemic stroke in patients presenting within 12 hours of symptom onset (Level A).**
- There is insufficient evidence to support or refute the value of PWI in diagnosing acute ischemic stroke (Level U).
- Baseline DWI volume should be considered useful in predicting baseline clinical stroke severity and final lesion volume in anterior-circulation stroke syndromes (Level B).

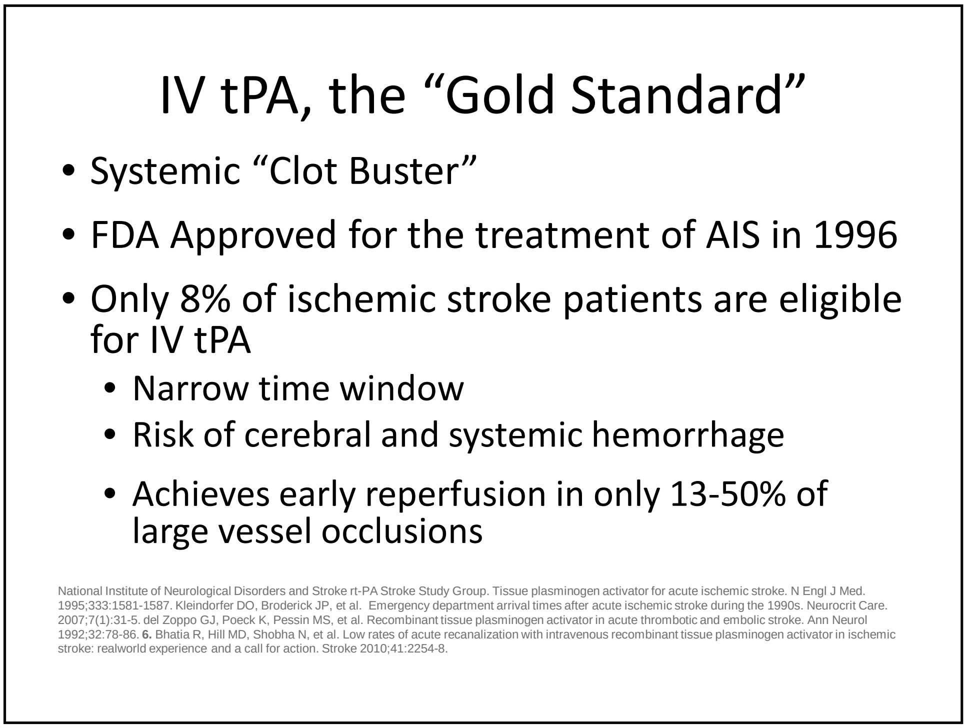
NEUROLOGY 2010;75:177-185



Acute Ischemic Stroke: ASA/AAN/ACCP Guidelines

- Pharmacotherapies
  - tPA (tissue plasminogen activator) within 3 hours of stroke onset
  - Aspirin for acute stroke (within 48 hours of symptom onset): 160 to 325 mg/day) (Grade 1A) to reduce stroke mortality and decrease morbidity; ONLY if no contraindications or if patient will not be given rtPA[1]
  - Heparin and low molecular weight heparin (LMWH): not indicated and may increase bleeding complications;
  - LMWH and heparinoids may be considered for DVT prophylaxis in at-risk patients[1]
- Early consultation by neurologist or stroke team critical[2]

1. Coull BM et al. *Stroke*. 2002;33:1934-1942.
2. Adams HP et al. *Stroke*. 2003;34:1056-1083.



IV tPA, the "Gold Standard"

- Systemic "Clot Buster"
- FDA Approved for the treatment of AIS in 1996
- Only 8% of ischemic stroke patients are eligible for IV tPA
  - Narrow time window
  - Risk of cerebral and systemic hemorrhage
  - Achieves early reperfusion in only 13-50% of large vessel occlusions

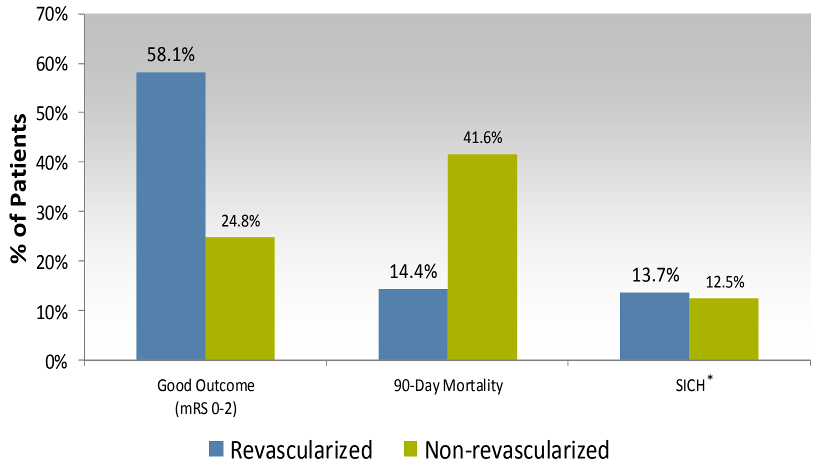
National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-1587. Kleindorfer DO, Broderick JP, et al. Emergency department arrival times after acute ischemic stroke during the 1990s. Neurocrit Care. 2007;7(1):31-5. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32:78-86. **6.** Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: realworld experience and a call for action. Stroke 2010;41:2254-8.

In patients with acute ischemic stroke:

- ≤ 3 hours for IV r-tPA (Grade 1A)
- 3 ≤ 4.5 hours we suggest IV r-tPA over no IV r-tPA (Grade 2C)
- Cannot be initiated ≤ 4.5 h of symptom onset, we recommend against IV r-tPA (Grade 1B)

CHEST. 2012;141(2_suppl):1S-1S. doi: 10.1378/chest.1412S1

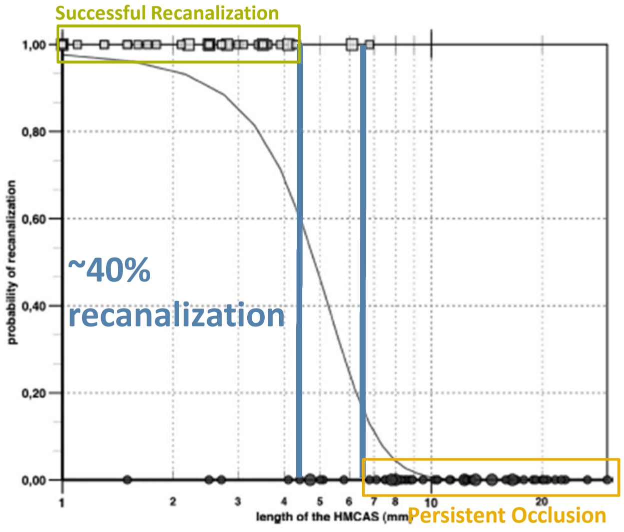
Meta-analysis Shows a Strong Correlation Between Revascularization and Good Patient Outcomes



*Differences in sICH were not statistically significant between the revascularized and non-revascularized groups

Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. 2007 Mar;38(3):967-73.

Impact of Clot Burden on Success Rate of IV tPA



Christian H. Riedel et. al. The Importance of Size: Successful Recanalization by Intravenous Thrombolysis in Acute Anterior Stroke Depends on Thrombus Length. Stroke, 2011;42:1775-1777

35-40% of Ischemic Strokes are Considered "Large Vessel"

- This subset of ischemic stroke comprises blockages in the:
  - Internal Carotid Artery (ICA)
  - Middle Cerebral Artery (MCA)
  - Vertebral / Basilar Artery
- Patient prognosis with these types of stroke is poor

Vessel	Mortality Rate
ICA	53%^{1}
MCA	27%^{2}
Basilar Artery	89-90%^{3}

1. Jansen O, et al.
2. Furlan A et al. PROACT II Trial
3. Brückmann H et al.

Turning Point

The Era of Stent-Retrievers

Technological advances

- Stent-retriever technology for safe, reliable performance
- Significant improvement in revascularization and patient outcomes vs older technology, proven in randomized clinical trials*

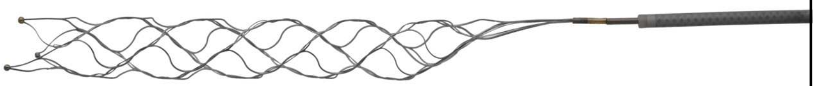


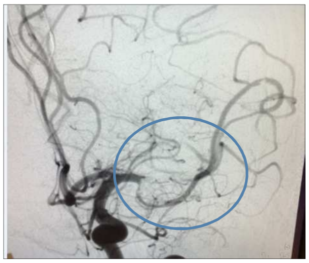
Image courtesy of Stryker Neurovascular.

* Raul G Nogueira, et. al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet, 2012; 380: 1231-40 and Jefferey L Saver et. al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Int J Stroke; 2012, 1747-4949

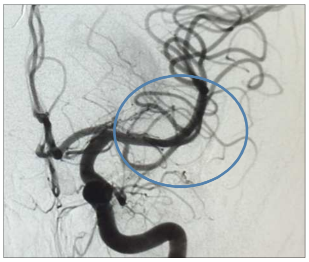
Trial Summary

Trial	Imaging Required to Confirm Occlusion Prior to Randomization?	Device(s) Used in Intervention Arm	TICI 2b/3 Revascularization Rate in the Intervention Arm	mRS 0-2		
				Intervention Arm	Control Arm	Odds Ratio (95% CI)
IMS III	No	IA Lytic (138), Merci Retriever® (95), EKOS (22), Penumbra (54), Solitaire FR (5)	38% ICA 44% M1 44% M2 23% multi M2	40.8% (N=415)	38.7% (N=214)	0.02 (-0.06 to 0.09)
MR RESCUE	No	Merci Retriever®, EKOS, IA Lytic, Penumbra	24% pen (n=34) 27% nonp (n=30)	21% pen (n=34) 17% nonp (n=30)	26% pen (n=34) 10% nonp (n=20)	NS
MR CLEAN	Yes	97% Stent Retrievers, 2% other Mechanical	58.7% (N=196)	33% (N=233)	19% (N=267)	2.16 (1.39-3.38)
ESCAPE	Yes	86% Stent Retriever	72.4% (n=156)	53.0% (n=164)	29.3% (n=147)	1.8 (1.4-2.4)
SWIFT PRIME	Yes	100% Stent Retriever	88.0% (n=83)	60.2% (n=98)	35.5% (n=93)	2.75 (1.53,4.95)
EXTEND-IA	Yes	100% Stent Retriever	86.2% (n=29)	71% (n=35)	40% (n=35)	4.2 (1.3-13)

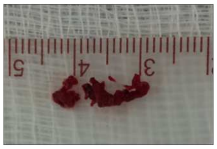
Goal of Ischemic Stroke Treatment



Before Intervention



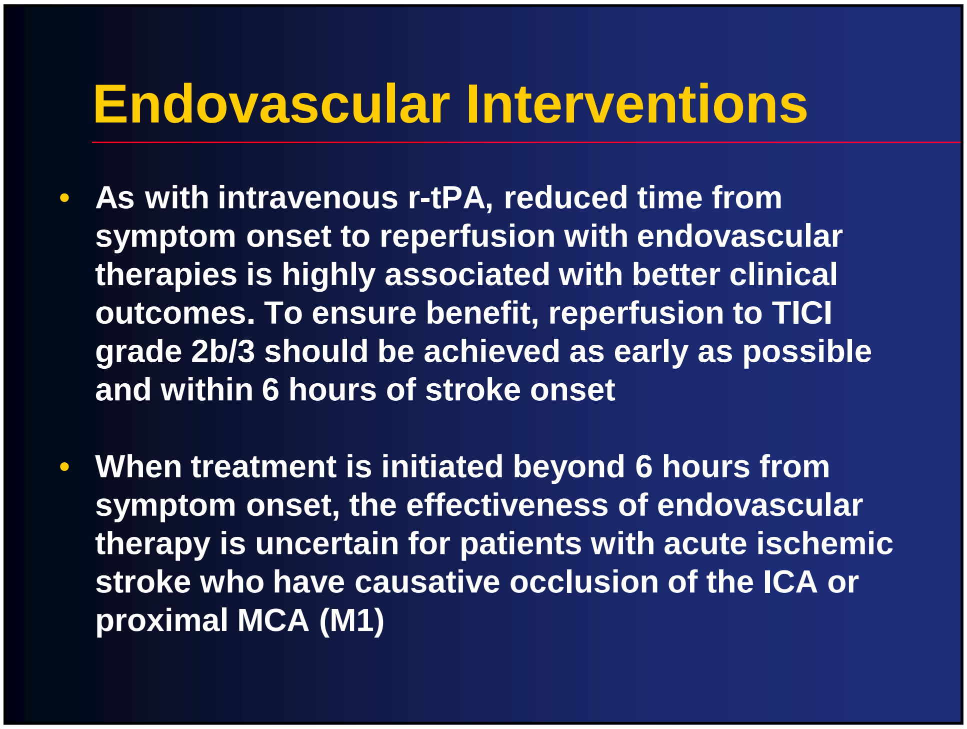
After Successful Intervention



Images courtesy of Dr. Joey English – Used with Permission. Results from case studies are not predictive of results in other cases. Results in other cases may vary.

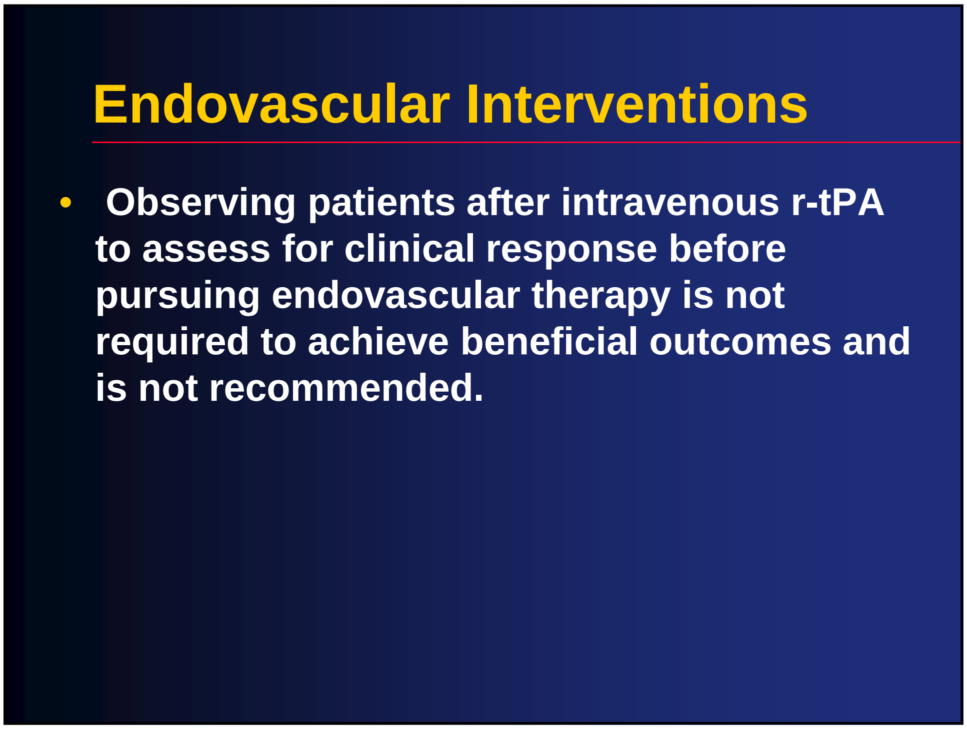
Endovascular Interventions

- Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered
- Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria
  - Prestroke mRS score 0 to 1
  - Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies
  - Causative occlusion of the ICA or proximal MCA (M1)
  - Age ≥18 years
  - NIHSS score of ≥6
  - ASPECTS of ≥6 hours
  - Treatment can be initiated (groin puncture) within 6 hours of symptom onset



Endovascular Interventions

- As with intravenous r-tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset
- When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the ICA or proximal MCA (M1)



Endovascular Interventions

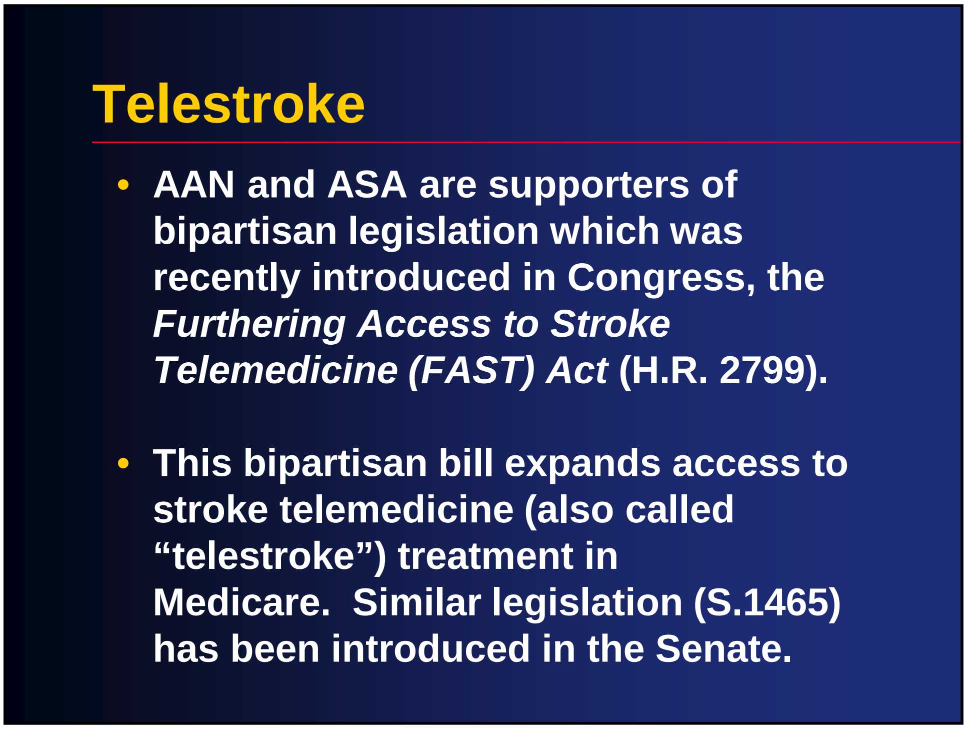
- Observing patients after intravenous r-tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended.

Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis

- Jeffrey L. Saver, MD[1]; Mayank Goyal, MD[2]; Aad van der Lugt, MD[3]; et al; for the HERMES Collaborators
- JAMA. 2016;316(12):1279-1288. doi:10.1001/jama.2016.13647
- In this individual patient data meta-analysis of patients with large-vessel ischemic stroke, earlier treatment with endovascular thrombectomy + medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months. Benefit became nonsignificant after 7.3 hours.

PHANTOM-S: The Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients - Study "PHANTOM-S"

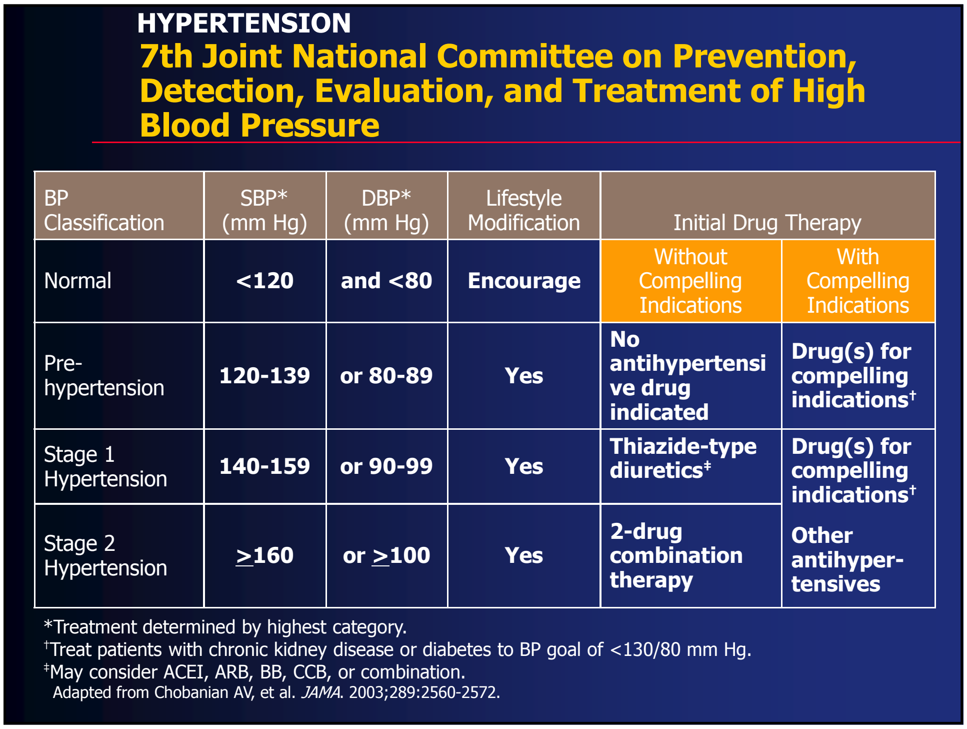
Lancet Neurol. 2012 May;11(5):397-404. doi: 10.1016/S1474-4422(12)70057-1. Epub 2012 Apr 11.



Telestroke

- AAN and ASA are supporters of bipartisan legislation which was recently introduced in Congress, the *Furthering Access to Stroke Telemedicine (FAST) Act* (H.R. 2799).
- This bipartisan bill expands access to stroke telemedicine (also called “telestroke”) treatment in Medicare. Similar legislation (S.1465) has been introduced in the Senate.

Lowering Blood Pressure



HYPERTENSION

7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

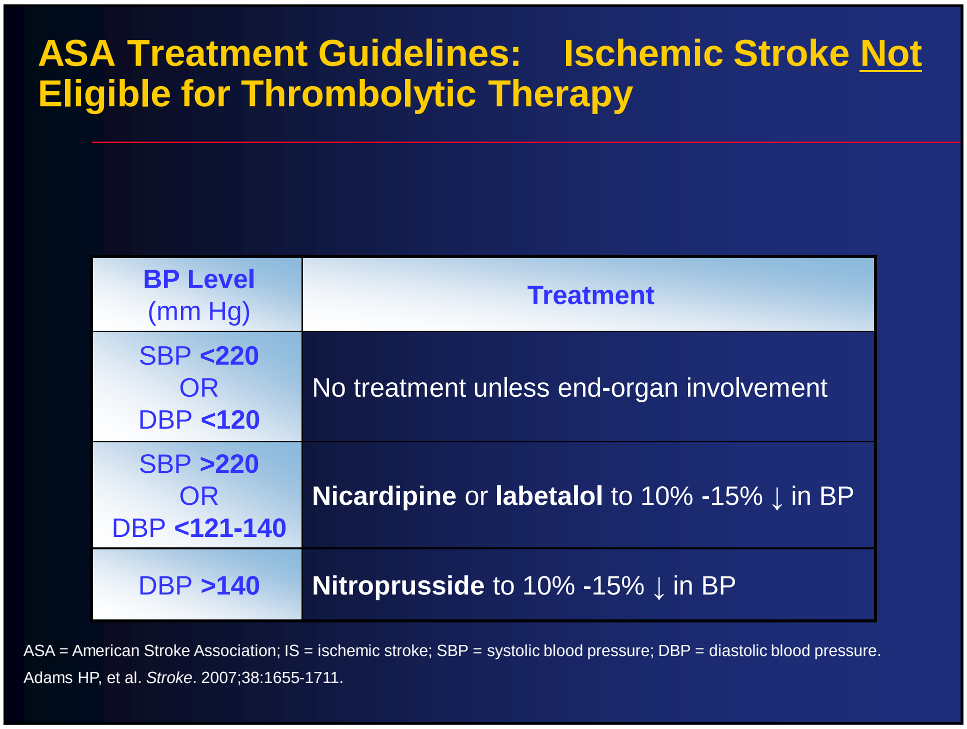
BP Classification	SBP* (mm Hg)	DBP* (mm Hg)	Lifestyle Modification	Initial Drug Therapy	
				Without Compelling Indications	With Compelling Indications
Normal	**<120**	**and <80**	**Encourage**		
Pre-hypertension	**120-139**	**or 80-89**	**Yes**	**No antihypertensive drug indicated**	**Drug(s) for compelling indications[†]**
Stage 1 Hypertension	**140-159**	**or 90-99**	**Yes**	**Thiazide-type diuretics[‡]**	**Drug(s) for compelling indications[†]** **Other antihyper-tensives**
Stage 2 Hypertension	**≥160**	**or ≥100**	**Yes**	**2-drug combination therapy**	

*Treatment determined by highest category.

[†] Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

[‡] May consider ACEI, ARB, BB, CCB, or combination.

Adapted from Chobanian AV, et al. *JAMA*. 2003;289:2560-2572.

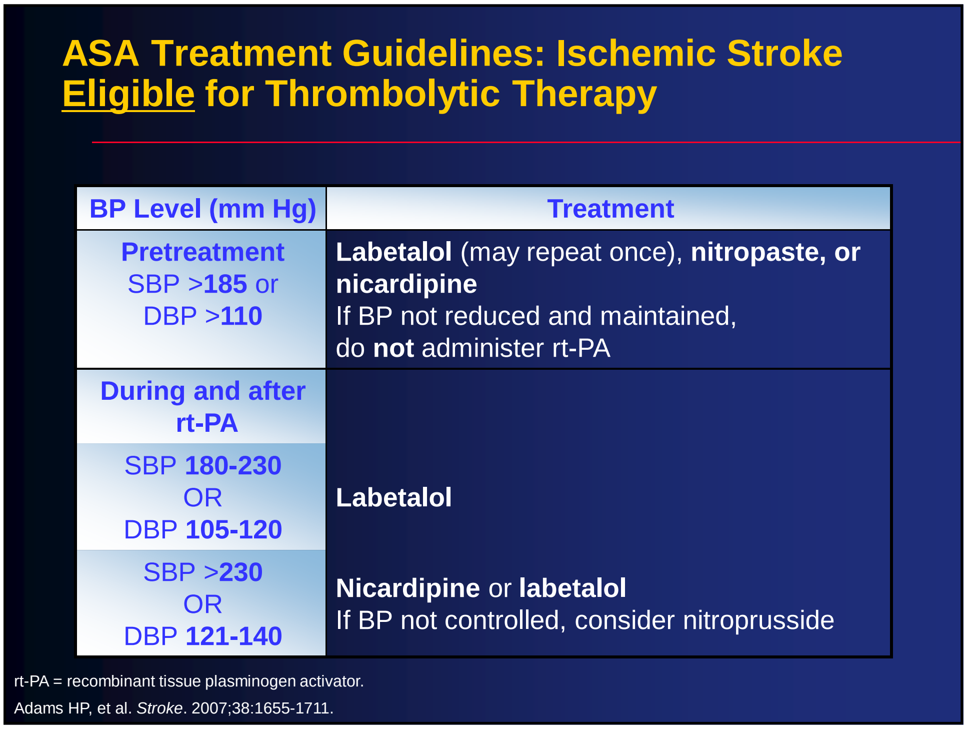


ASA Treatment Guidelines: Ischemic Stroke Not Eligible for Thrombolytic Therapy

BP Level (mm Hg)	**Treatment**
SBP **<220** OR DBP **<120**	No treatment unless end-organ involvement
SBP **>220** OR DBP **<121-140**	**Nicardipine** or **labetalol** to 10% -15% ↓ in BP
DBP **>140**	**Nitroprusside** to 10% -15% ↓ in BP

ASA = American Stroke Association; IS = ischemic stroke; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Adams HP, et al. *Stroke*. 2007;38:1655-1711.

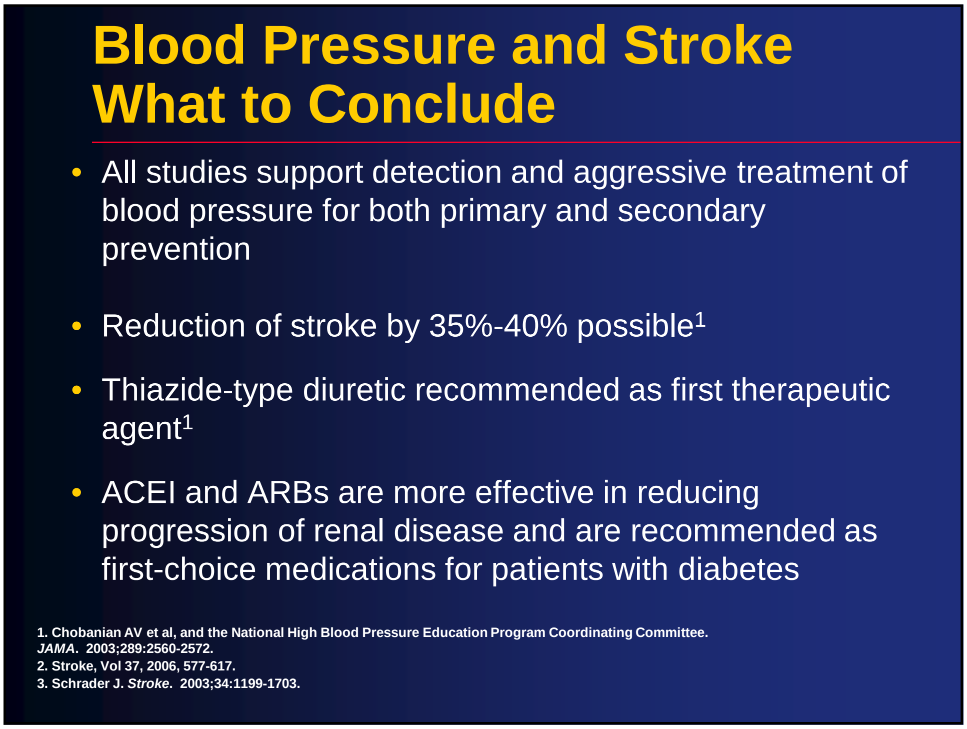


ASA Treatment Guidelines: Ischemic Stroke Eligible for Thrombolytic Therapy

BP Level (mm Hg)	Treatment
Pretreatment SBP >**185** or DBP >**110**	**Labetalol** (may repeat once), **nitropaste, or nicardipine** If BP not reduced and maintained, do **not** administer rt-PA
During and after rt-PA	
SBP **180-230** OR DBP **105-120**	**Labetalol**
SBP >**230** OR DBP **121-140**	**Nicardipine** or **labetalol** If BP not controlled, consider nitroprusside

rt-PA = recombinant tissue plasminogen activator.

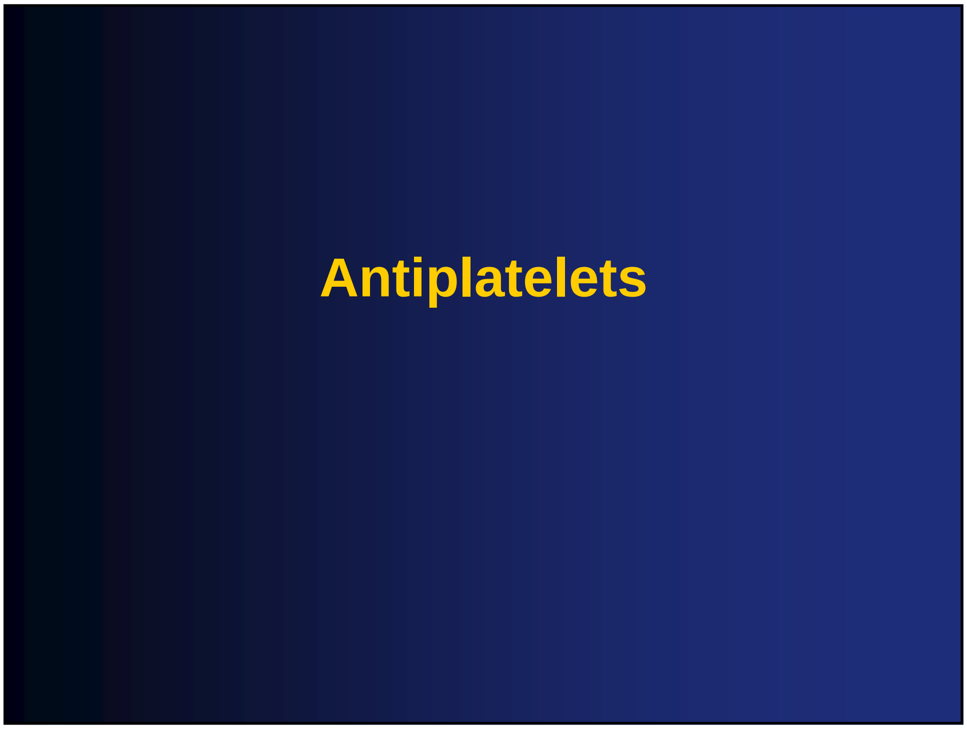
Adams HP, et al. *Stroke*. 2007;38:1655-1711.



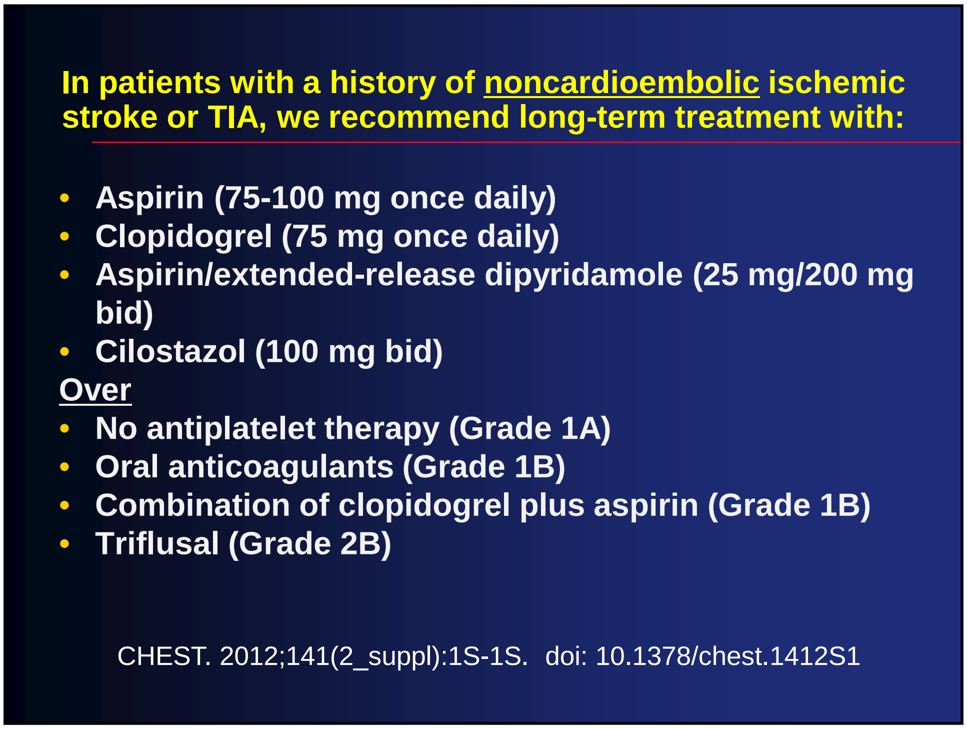
Blood Pressure and Stroke What to Conclude

- All studies support detection and aggressive treatment of blood pressure for both primary and secondary prevention
- Reduction of stroke by 35%-40% possible[1]
- Thiazide-type diuretic recommended as first therapeutic agent[1]
- ACEI and ARBs are more effective in reducing progression of renal disease and are recommended as first-choice medications for patients with diabetes

1. Chobanian AV et al, and the National High Blood Pressure Education Program Coordinating Committee. *JAMA*. 2003;289:2560-2572.
2. Stroke, Vol 37, 2006, 577-617.
3. Schrader J. *Stroke*. 2003;34:1199-1703.



Antiplatelets



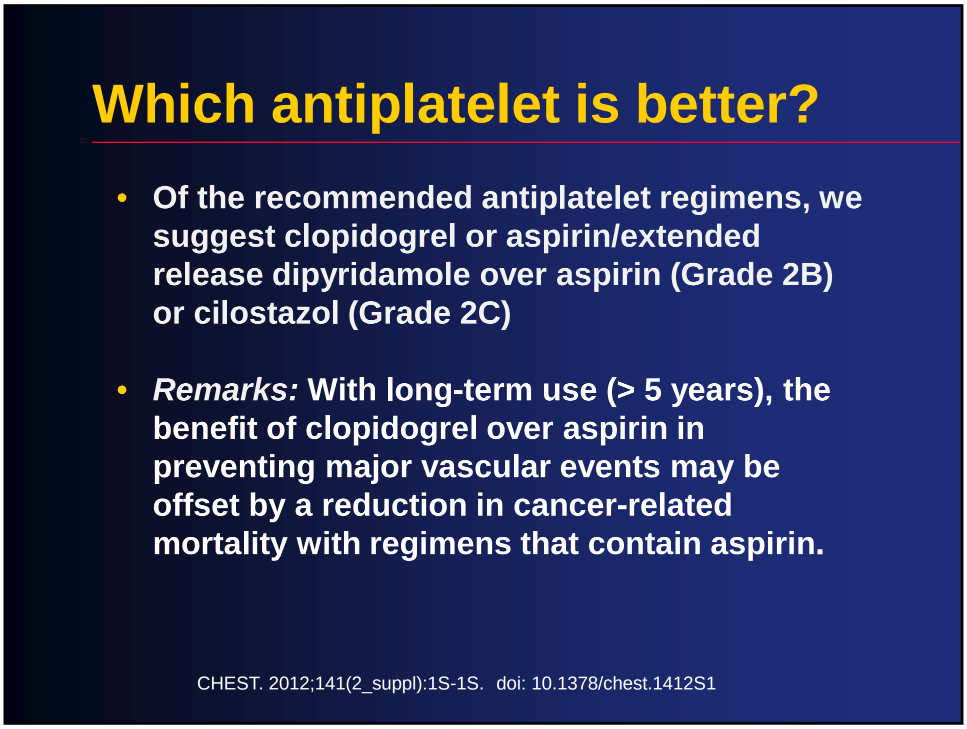
In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend long-term treatment with:

- **Aspirin (75-100 mg once daily)**
- **Clopidogrel (75 mg once daily)**
- **Aspirin/extended-release dipyridamole (25 mg/200 mg bid)**
- **Cilostazol (100 mg bid)**

Over

- **No antiplatelet therapy (Grade 1A)**
- **Oral anticoagulants (Grade 1B)**
- **Combination of clopidogrel plus aspirin (Grade 1B)**
- **Triflusal (Grade 2B)**

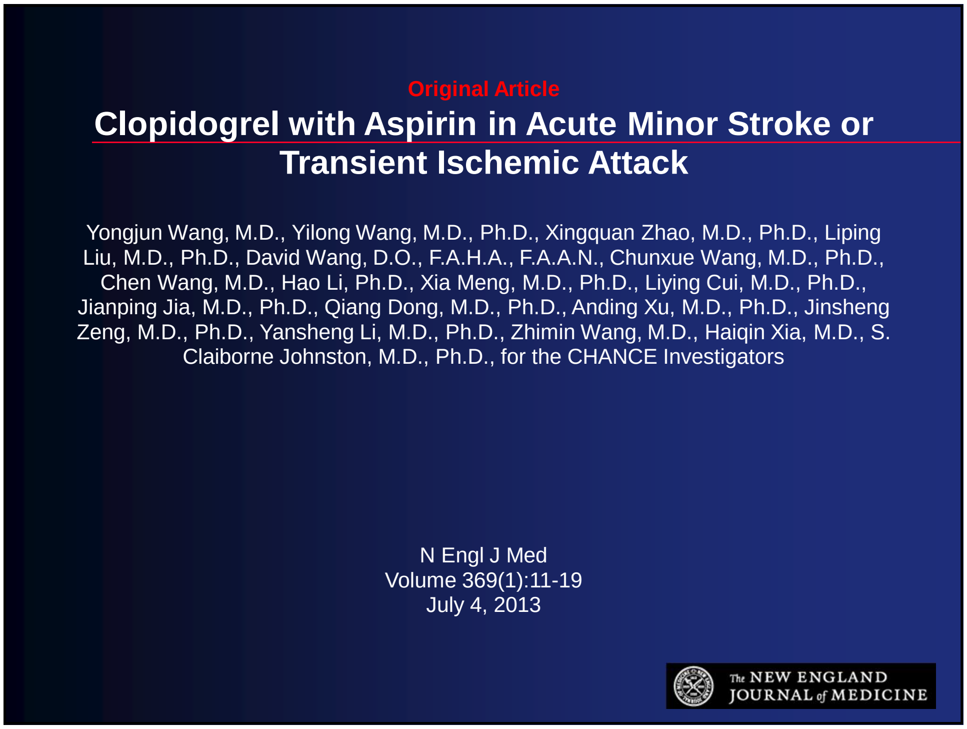
CHEST. 2012;141(2_suppl):1S-1S. doi: 10.1378/chest.1412S1



Which antiplatelet is better?

- Of the recommended antiplatelet regimens, we suggest clopidogrel or aspirin/extended release dipyridamole over aspirin (Grade 2B) or cilostazol (Grade 2C)
- *Remarks:* With long-term use (> 5 years), the benefit of clopidogrel over aspirin in preventing major vascular events may be offset by a reduction in cancer-related mortality with regimens that contain aspirin.

CHEST. 2012;141(2_suppl):1S-1S. doi: 10.1378/chest.1412S1



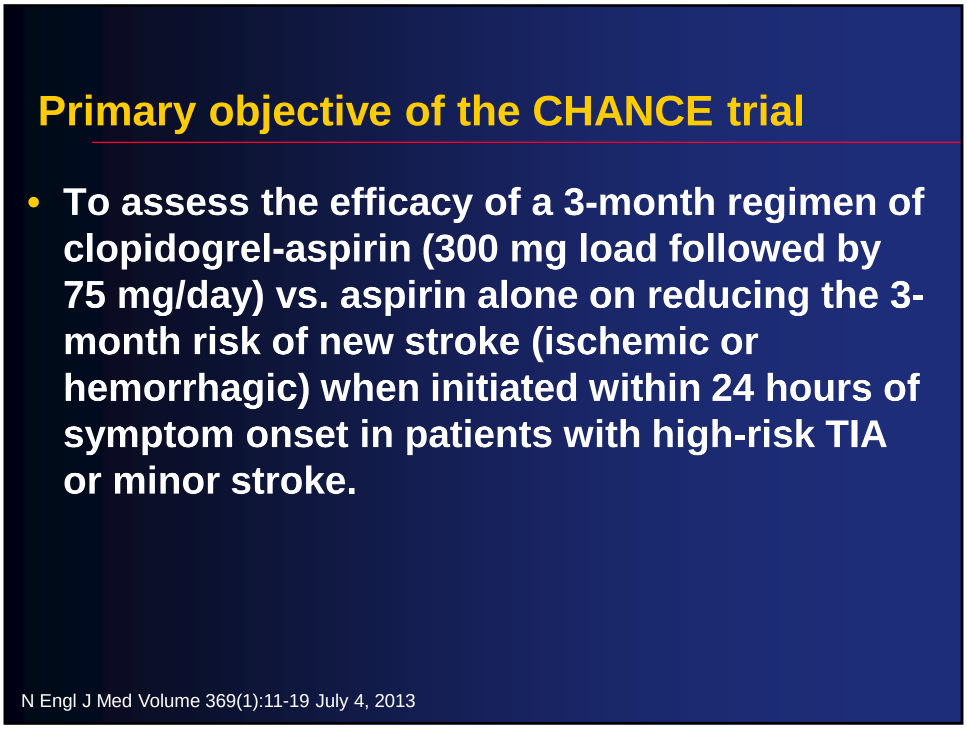
Original Article

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liying Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators

N Engl J Med
Volume 369(1):11-19
July 4, 2013

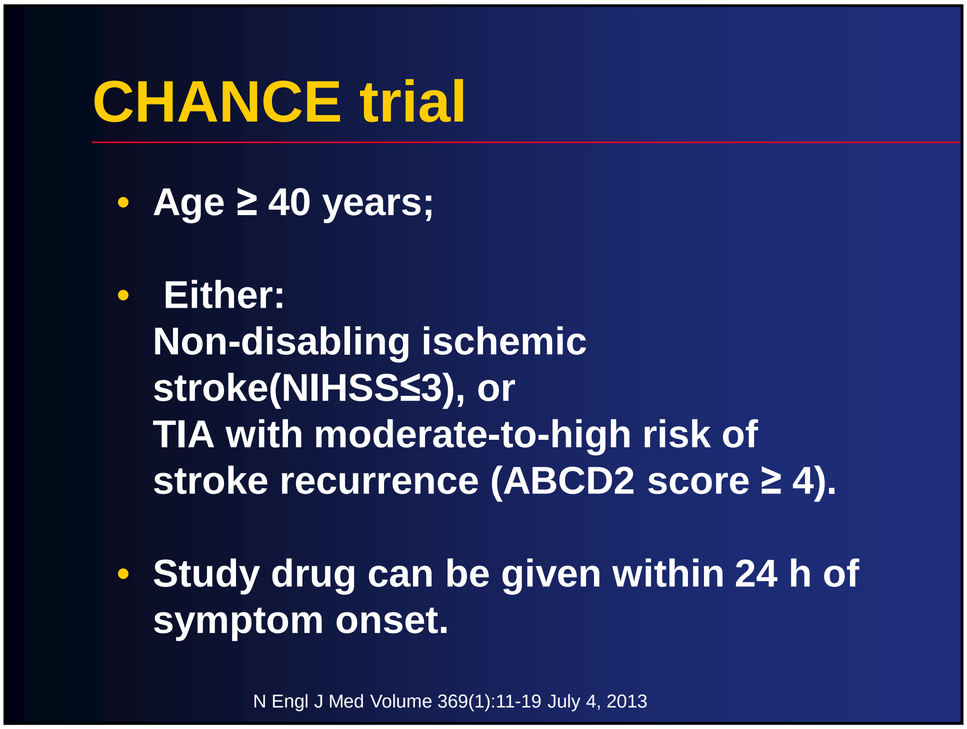
The NEW ENGLAND JOURNAL of MEDICINE



Primary objective of the CHANCE trial

- To assess the efficacy of a 3-month regimen of clopidogrel-aspirin (300 mg load followed by 75 mg/day) vs. aspirin alone on reducing the 3-month risk of new stroke (ischemic or hemorrhagic) when initiated within 24 hours of symptom onset in patients with high-risk TIA or minor stroke.

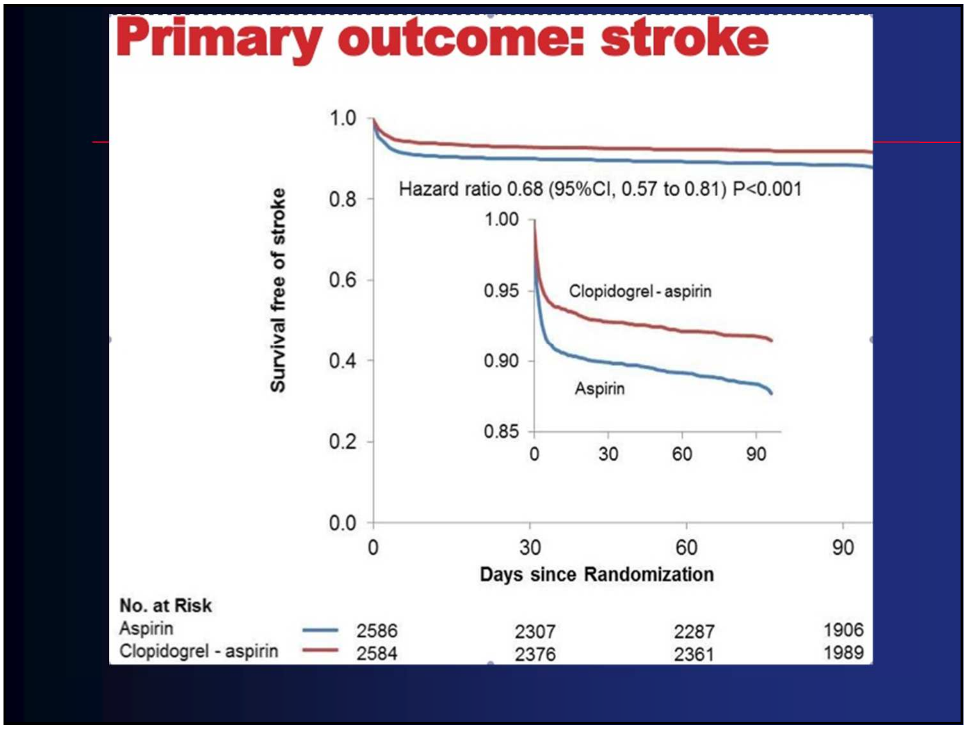
N Engl J Med Volume 369(1):11-19 July 4, 2013



CHANCE trial

- Age ≥ 40 years;
- Either:
  Non-disabling ischemic stroke(NIHSS≤3), or
  TIA with moderate-to-high risk of stroke recurrence (ABCD2 score ≥ 4).
- Study drug can be given within 24 h of symptom onset.

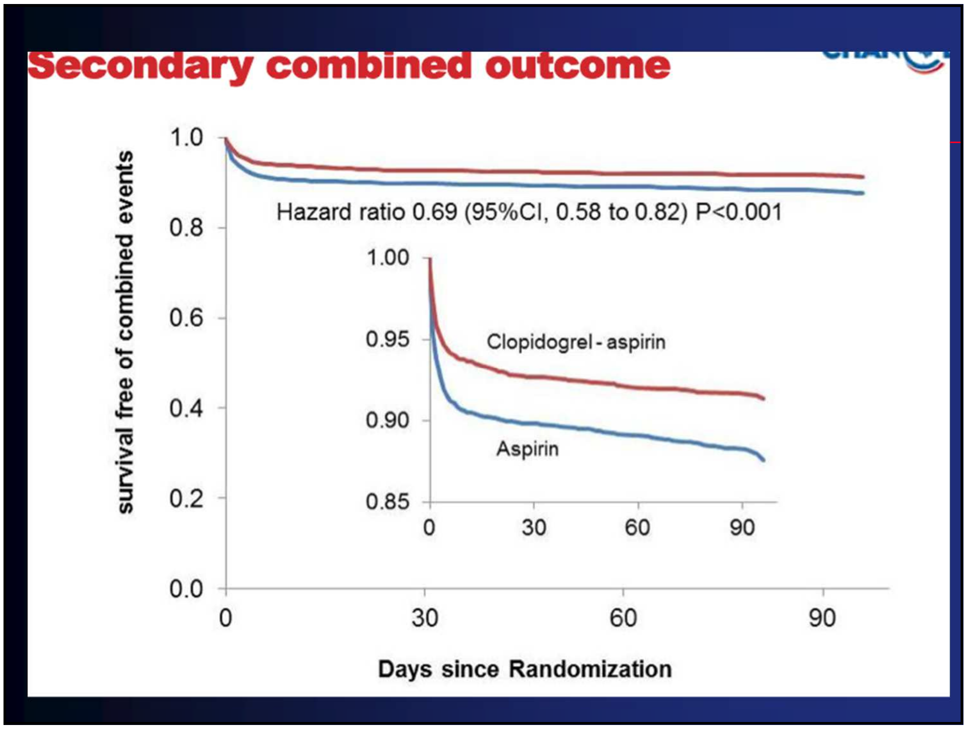
N Engl J Med Volume 369(1):11-19 July 4, 2013



Primary outcome: stroke

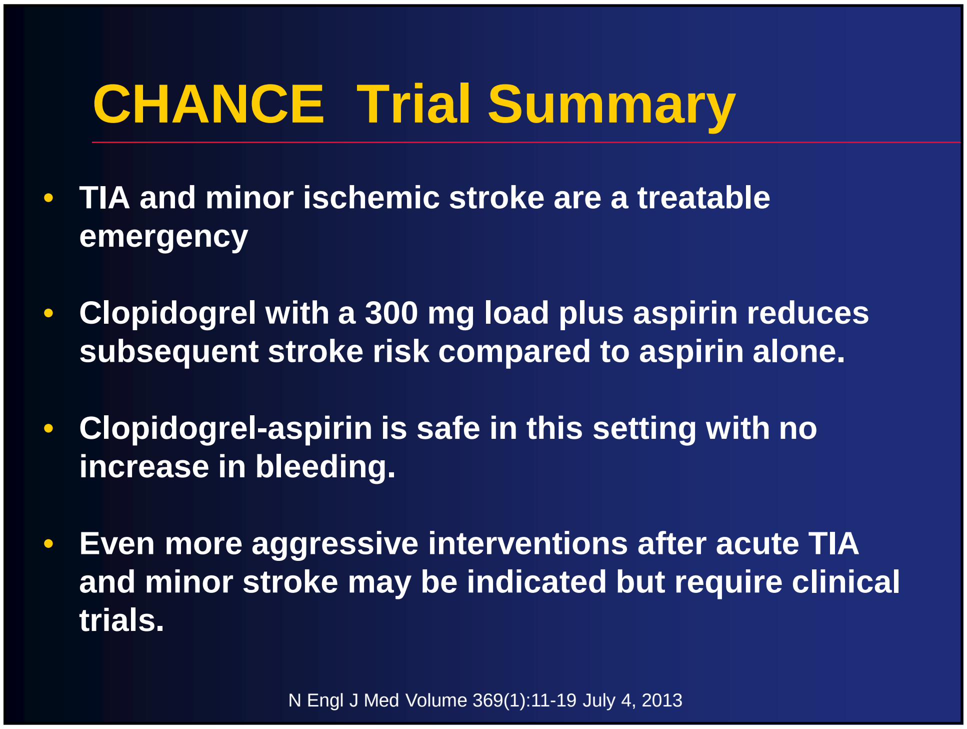
Hazard ratio 0.68 (95%CI, 0.57 to 0.81) P<0.001

No. at Risk				
Aspirin	2586	2307	2287	1906
Clopidogrel - aspirin	2584	2376	2361	1989



Secondary combined outcome

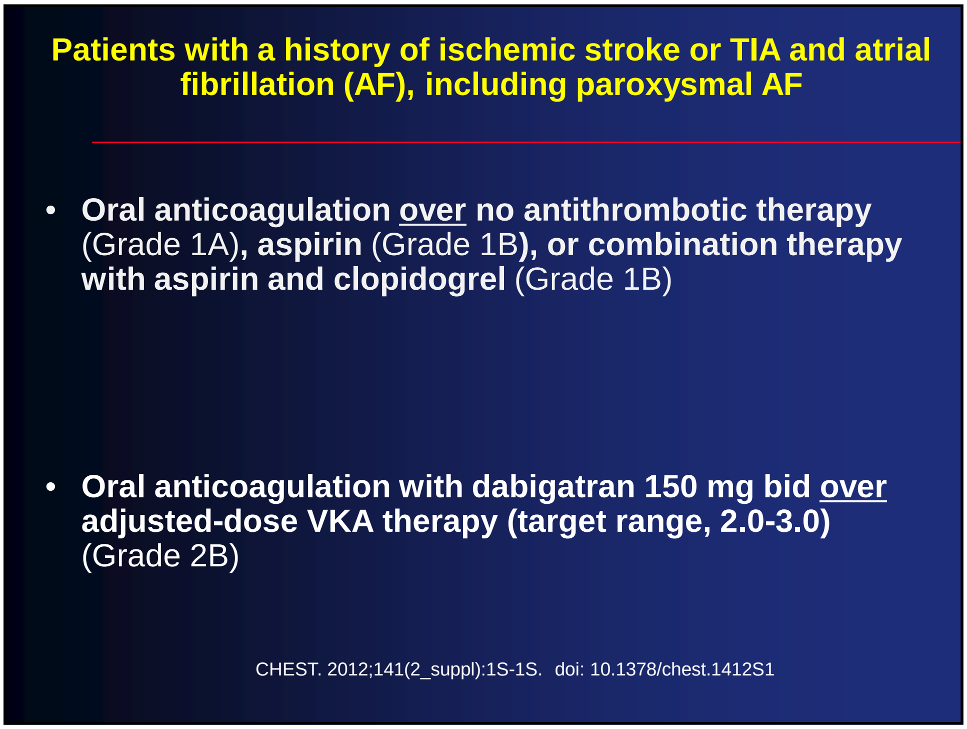
Hazard ratio 0.69 (95%CI, 0.58 to 0.82) P<0.001



CHANCE Trial Summary

- **TIA and minor ischemic stroke are a treatable emergency**
- **Clopidogrel with a 300 mg load plus aspirin reduces subsequent stroke risk compared to aspirin alone.**
- **Clopidogrel-aspirin is safe in this setting with no increase in bleeding.**
- **Even more aggressive interventions after acute TIA and minor stroke may be indicated but require clinical trials.**

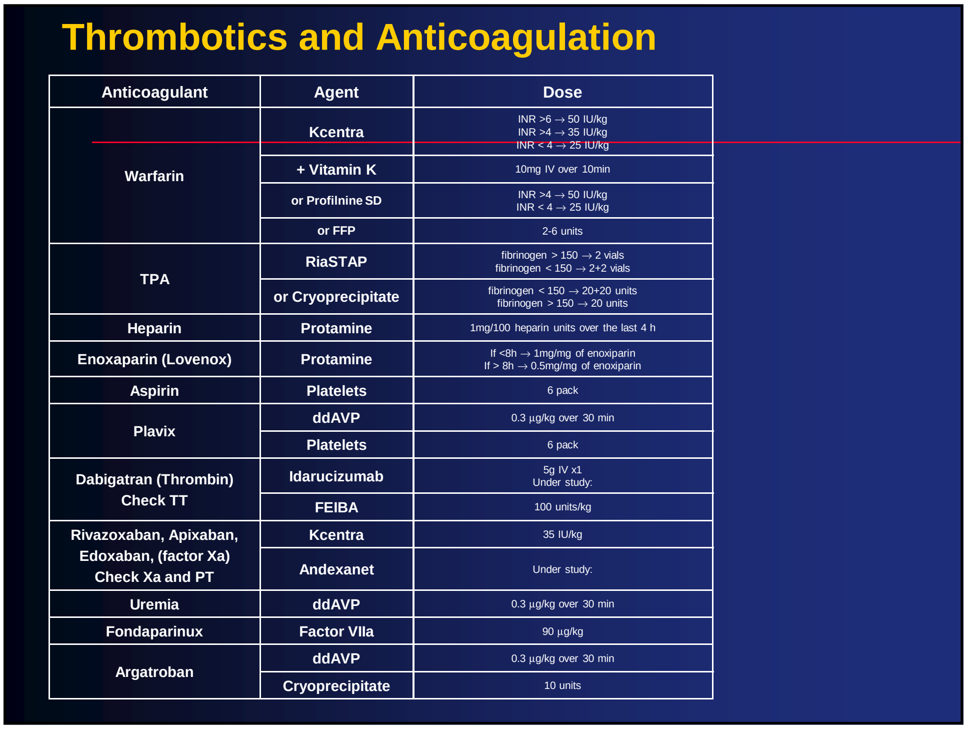
N Engl J Med Volume 369(1):11-19 July 4, 2013



Patients with a history of ischemic stroke or TIA and atrial fibrillation (AF), including paroxysmal AF

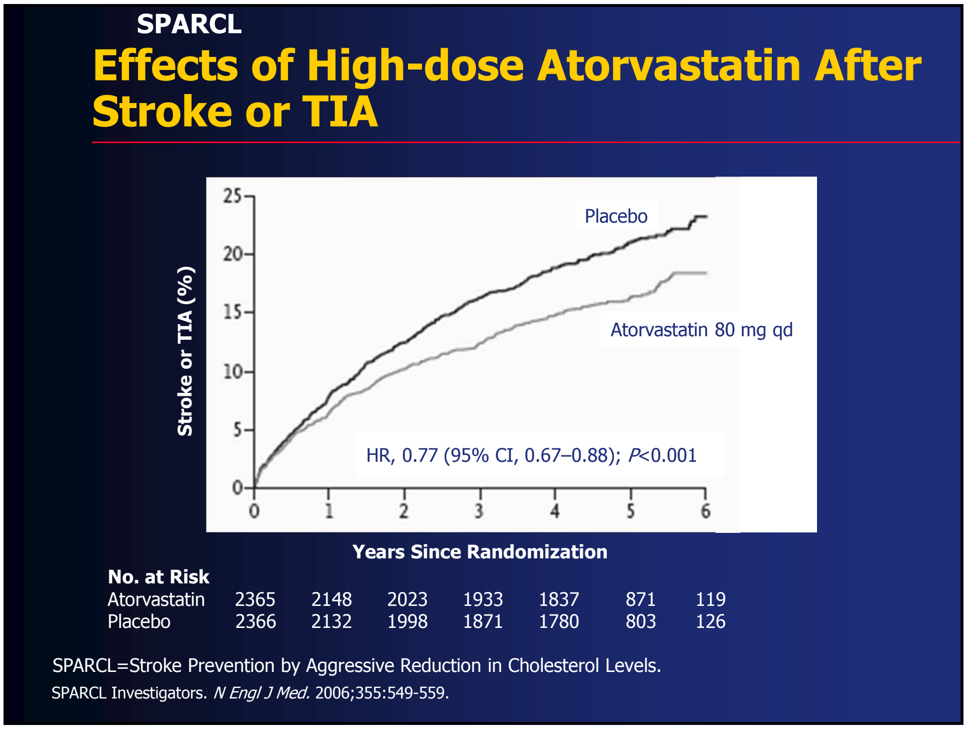
- **Oral anticoagulation over no antithrombotic therapy** (Grade 1A)**, aspirin** (Grade 1B)**, or combination therapy with aspirin and clopidogrel** (Grade 1B)
- **Oral anticoagulation with dabigatran 150 mg bid over adjusted-dose VKA therapy (target range, 2.0-3.0)** (Grade 2B)

CHEST. 2012;141(2_suppl):1S-1S. doi: 10.1378/chest.1412S1



Thrombotics and Anticoagulation

Anticoagulant	Agent	Dose
Warfarin	Kcentra	INR >6 → 50 IU/kg INR >4 → 35 IU/kg INR < 4 → 25 IU/kg
	+ Vitamin K	10mg IV over 10min
	or Profilnine SD	INR >4 → 50 IU/kg INR < 4 → 25 IU/kg
	or FFP	2-6 units
TPA	RiaSTAP	fibrinogen > 150 → 2 vials fibrinogen < 150 → 2+2 vials
	or Cryoprecipitate	fibrinogen < 150 → 20+20 units fibrinogen > 150 → 20 units
Heparin	Protamine	1mg/100 heparin units over the last 4 h
Enoxaparin (Lovenox)	Protamine	If <8h → 1mg/mg of enoxiparin If > 8h → 0.5mg/mg of enoxiparin
Aspirin	Platelets	6 pack
Plavix	ddAVP	0.3 µg/kg over 30 min
	Platelets	6 pack
Dabigatran (Thrombin) Check TT	Idarucizumab	5g IV x1 Under study:
	FEIBA	100 units/kg
Rivazoxaban, Apixaban, Edoxaban, (factor Xa) Check Xa and PT	Kcentra	35 IU/kg
	Andexanet	Under study:
Uremia	ddAVP	0.3 µg/kg over 30 min
Fondaparinux	Factor VIIa	90 µg/kg
Argatroban	ddAVP	0.3 µg/kg over 30 min
	Cryoprecipitate	10 units



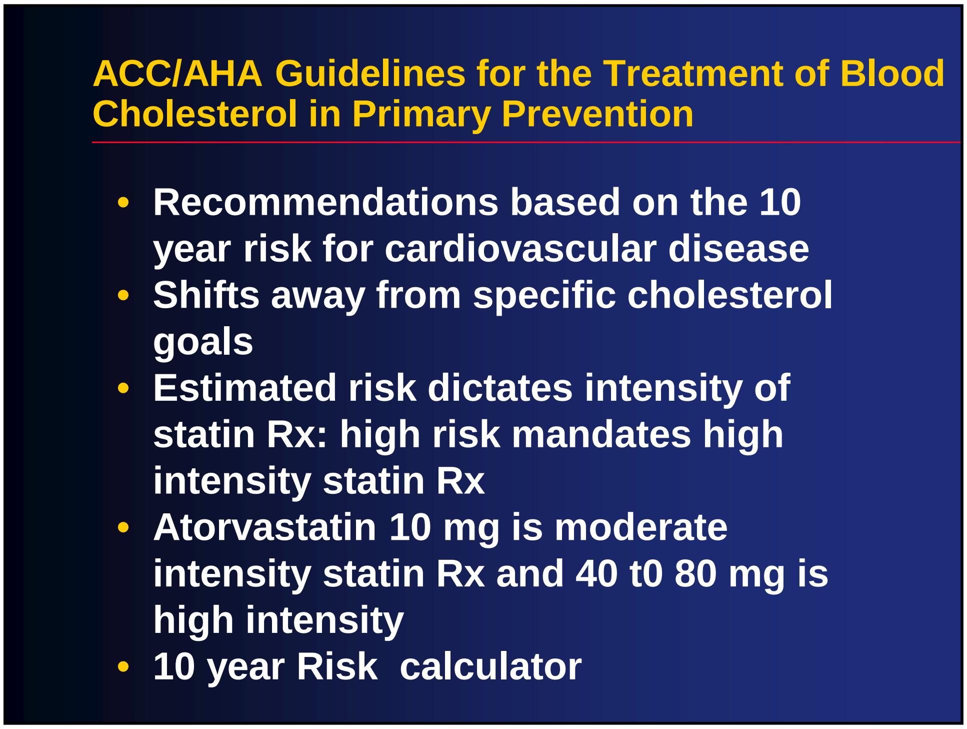
SPARCL

Effects of High-dose Atorvastatin After Stroke or TIA

No. at Risk							
Atorvastatin	2365	2148	2023	1933	1837	871	119
Placebo	2366	2132	1998	1871	1780	803	126

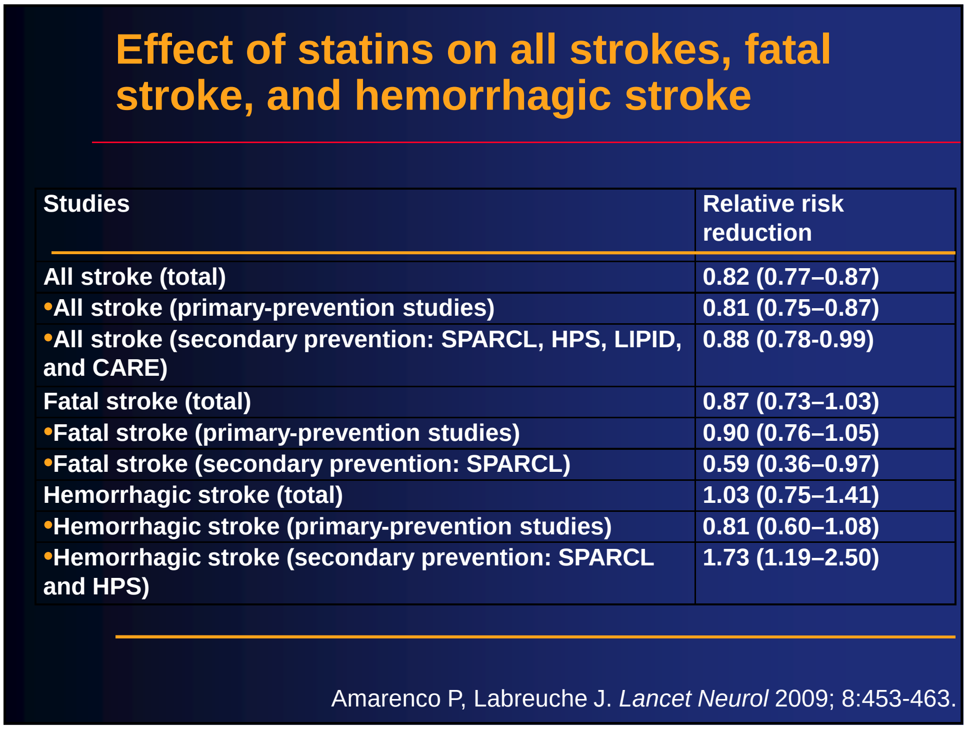
SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

SPARCL Investigators. *N Engl J Med.* 2006;355:549-559.



ACC/AHA Guidelines for the Treatment of Blood Cholesterol in Primary Prevention

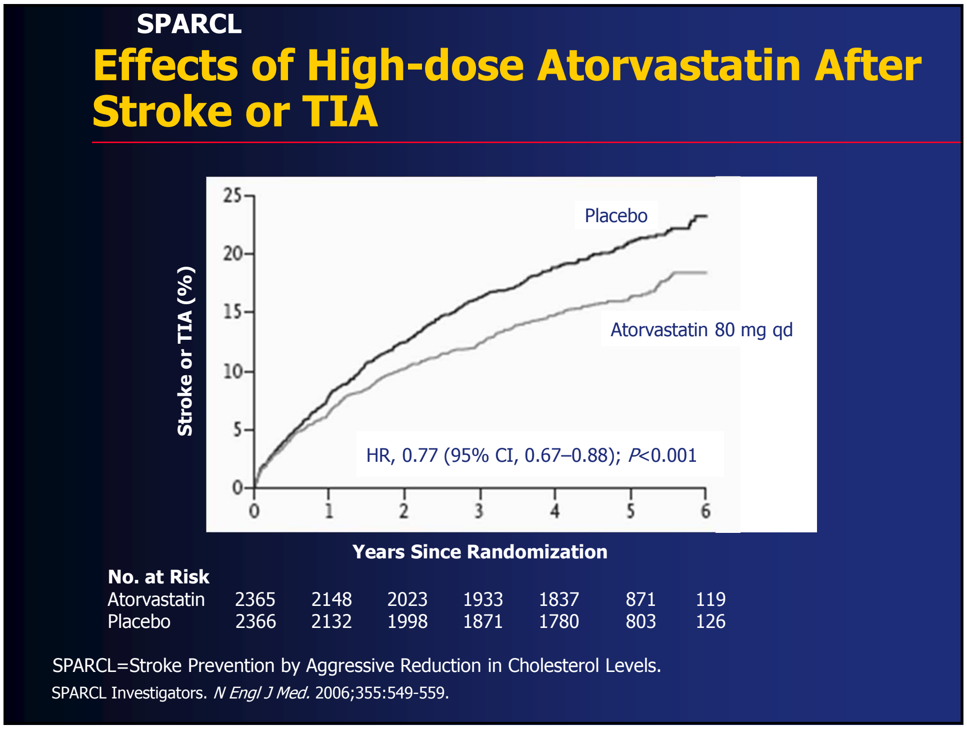
- Recommendations based on the 10 year risk for cardiovascular disease
- Shifts away from specific cholesterol goals
- Estimated risk dictates intensity of statin Rx: high risk mandates high intensity statin Rx
- Atorvastatin 10 mg is moderate intensity statin Rx and 40 t0 80 mg is high intensity
- 10 year Risk calculator



Effect of statins on all strokes, fatal stroke, and hemorrhagic stroke

Studies	Relative risk reduction
All stroke (total)	0.82 (0.77–0.87)
•All stroke (primary-prevention studies)	0.81 (0.75–0.87)
•All stroke (secondary prevention: SPARCL, HPS, LIPID, and CARE)	0.88 (0.78-0.99)
Fatal stroke (total)	0.87 (0.73–1.03)
•Fatal stroke (primary-prevention studies)	0.90 (0.76–1.05)
•Fatal stroke (secondary prevention: SPARCL)	0.59 (0.36–0.97)
Hemorrhagic stroke (total)	1.03 (0.75–1.41)
•Hemorrhagic stroke (primary-prevention studies)	0.81 (0.60–1.08)
•Hemorrhagic stroke (secondary prevention: SPARCL and HPS)	1.73 (1.19–2.50)

Amarenco P, Labreuche J. *Lancet Neurol* 2009; 8:453-463.



SPARCL

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SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

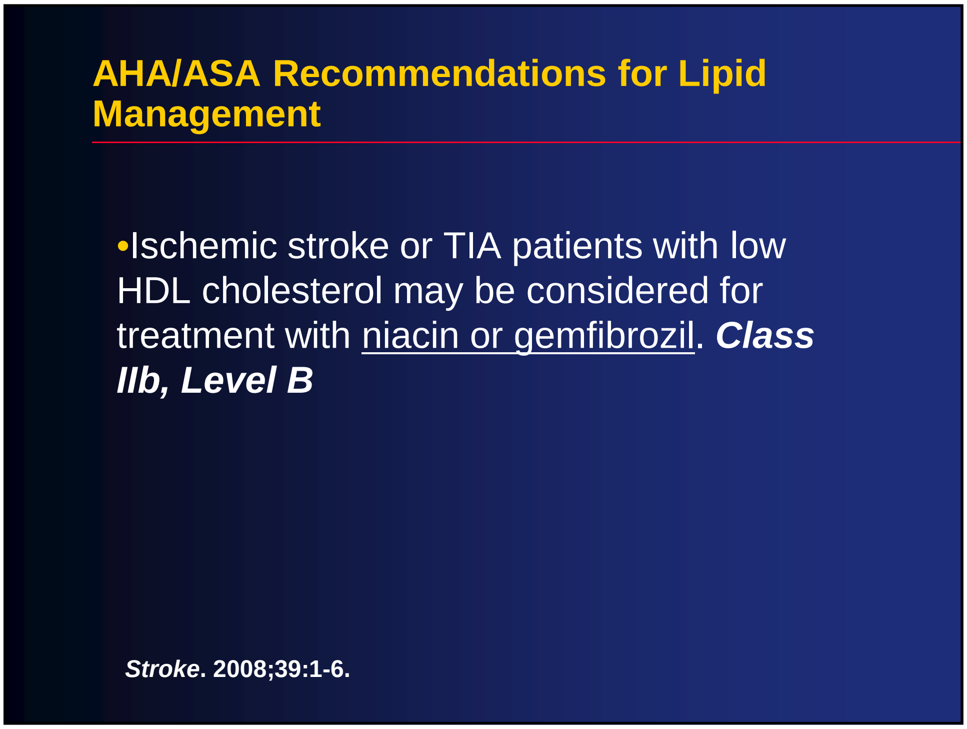
SPARCL Investigators. *N Engl J Med.* 2006;355:549-559.

AHA/ASA Recommendations for Lipid Management

- Ischemic stroke or TIA patients with elevated cholesterol, comorbid coronary artery disease, or evidence of an atherosclerotic origin should be managed according to NCEP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations. ***Class I, Level A***

- Statin agents are recommended, and the target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C level of **100 mg/dL**. An LDL-C **70 mg/dL** is recommended for very high-risk persons with multiple risk factors. ***Class I, Level A***

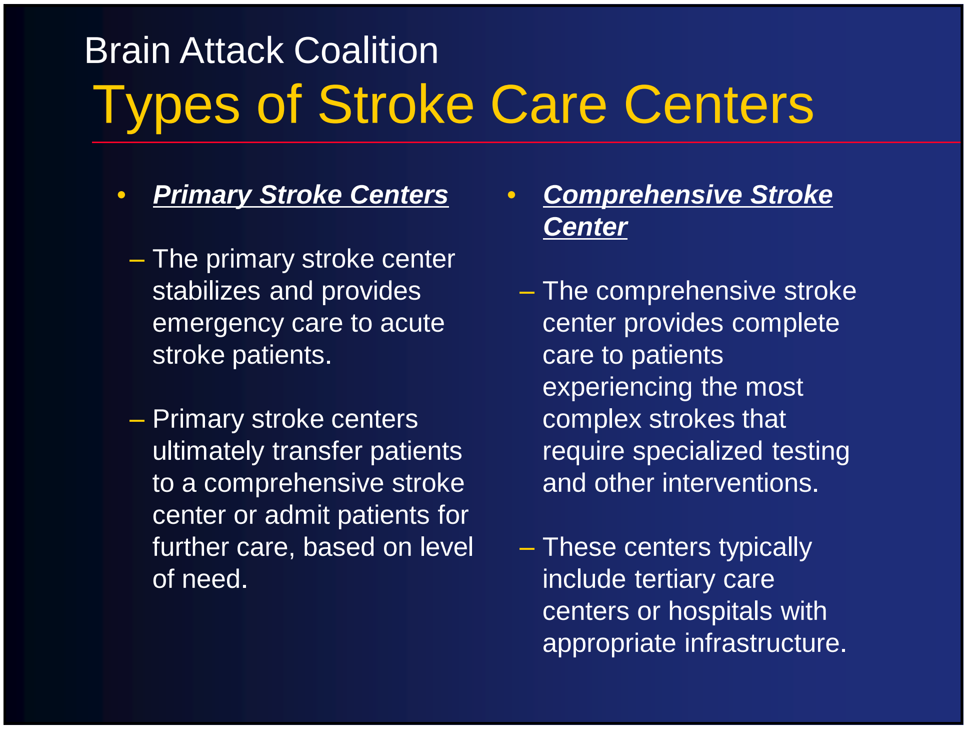
***Stroke*. 2008;39:1-6.**



AHA/ASA Recommendations for Lipid Management

- Ischemic stroke or TIA patients with low HDL cholesterol may be considered for treatment with niacin or gemfibrozil. ***Class IIb, Level B***

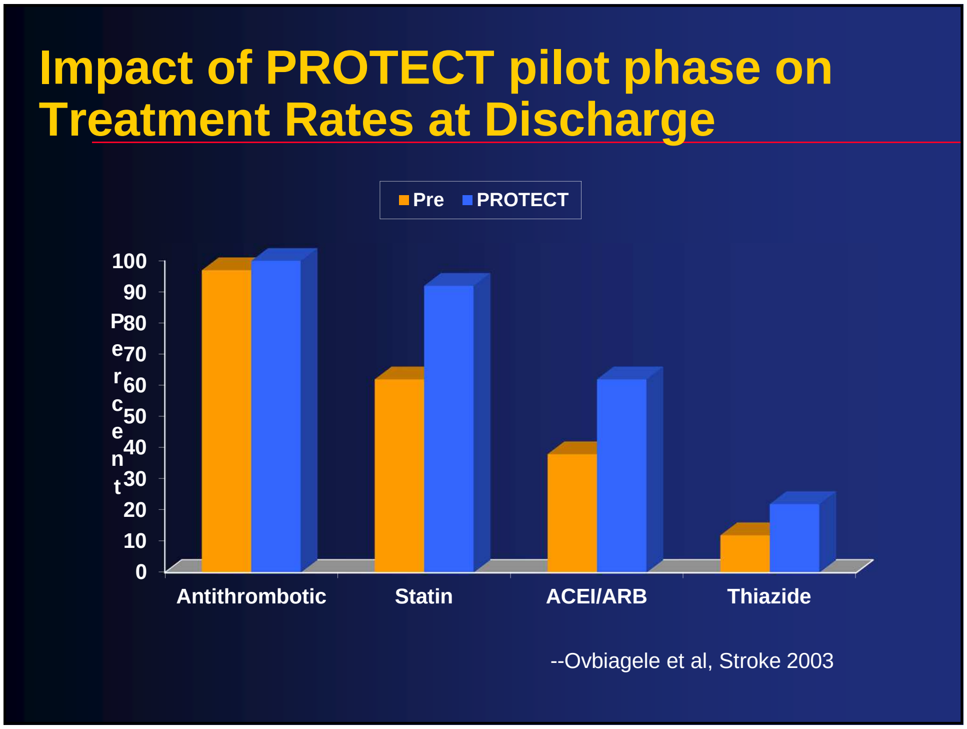
***Stroke*. 2008;39:1-6.**



Brain Attack Coalition

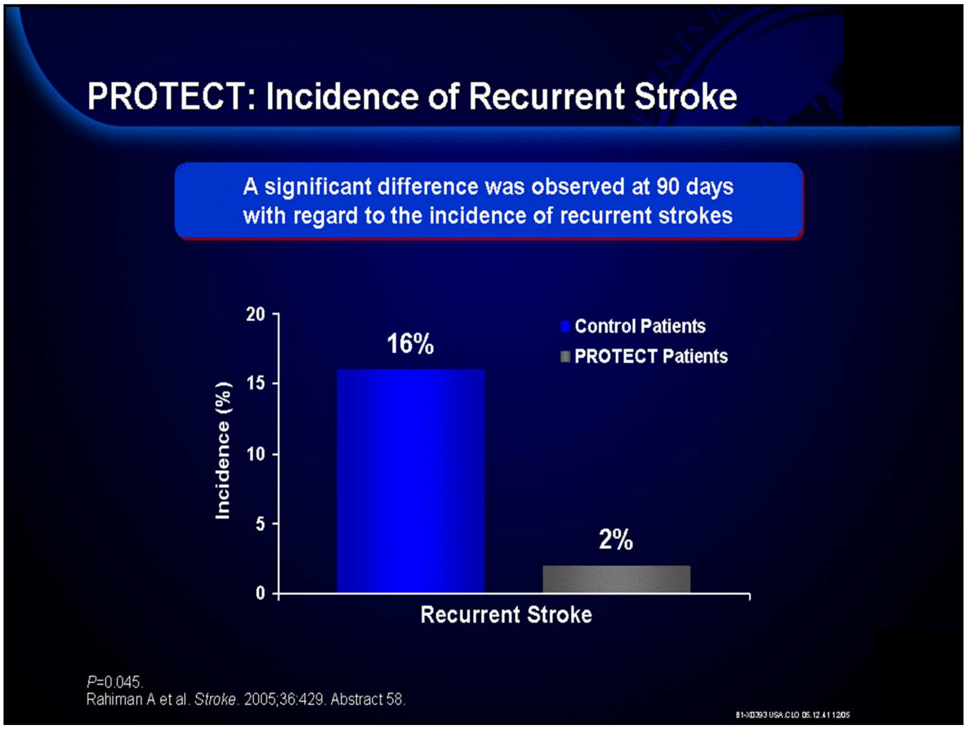
Types of Stroke Care Centers

- ***Primary Stroke Centers***
  - The primary stroke center stabilizes and provides emergency care to acute stroke patients.
  - Primary stroke centers ultimately transfer patients to a comprehensive stroke center or admit patients for further care, based on level of need.
- ***Comprehensive Stroke Center***
  - The comprehensive stroke center provides complete care to patients experiencing the most complex strokes that require specialized testing and other interventions.
  - These centers typically include tertiary care centers or hospitals with appropriate infrastructure.



Impact of PROTECT pilot phase on Treatment Rates at Discharge

--Ovbiagele et al, Stroke 2003

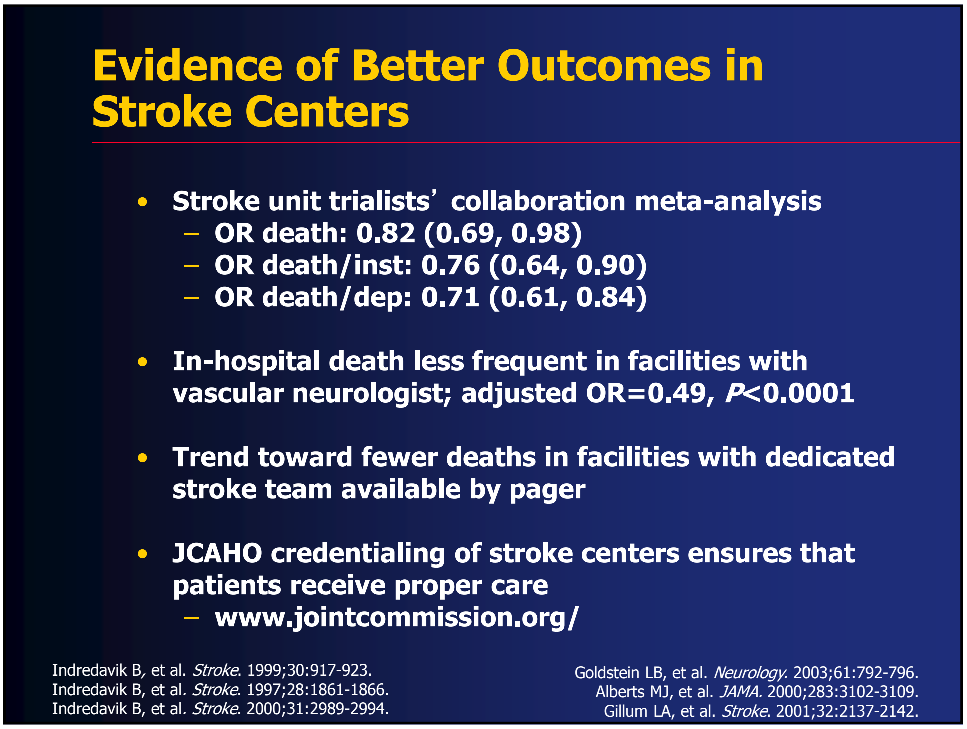


PROTECT: Incidence of Recurrent Stroke

A significant difference was observed at 90 days with regard to the incidence of recurrent strokes

P=0.045.
Rahiman A et al. *Stroke*. 2005;36:429. Abstract 58.

81-X0393 USA.CLO 05.12.41 12/05

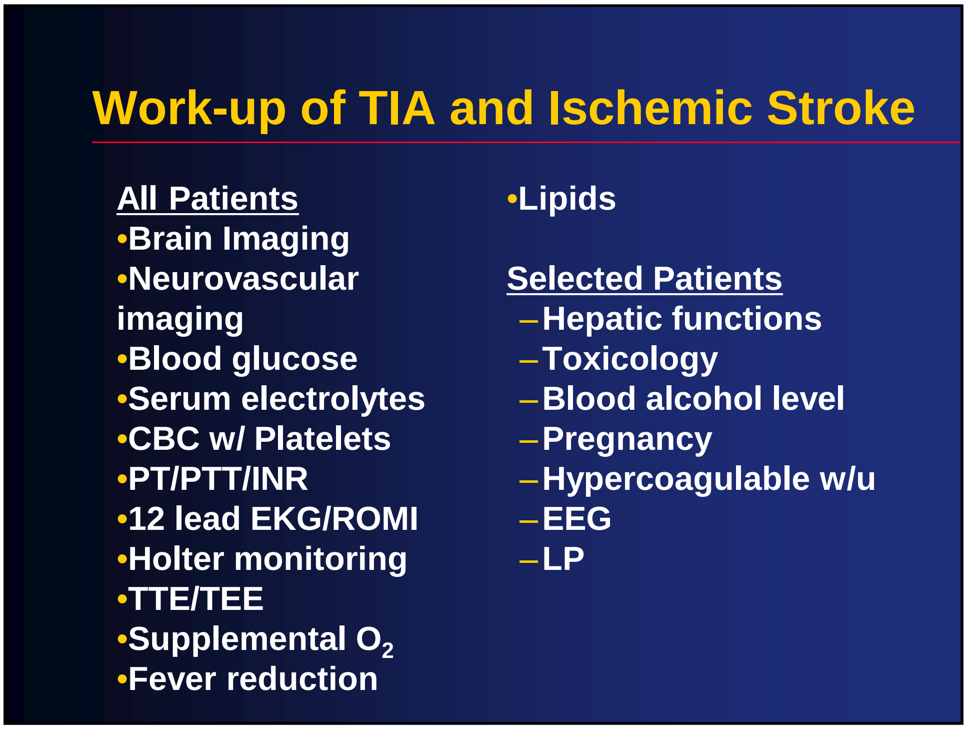


Evidence of Better Outcomes in Stroke Centers

- Stroke unit trialists' collaboration meta-analysis
  - OR death: 0.82 (0.69, 0.98)
  - OR death/inst: 0.76 (0.64, 0.90)
  - OR death/dep: 0.71 (0.61, 0.84)
- In-hospital death less frequent in facilities with vascular neurologist; adjusted OR=0.49, $P<0.0001$
- Trend toward fewer deaths in facilities with dedicated stroke team available by pager
- JCAHO credentialing of stroke centers ensures that patients receive proper care
  - www.jointcommission.org/

Indredavik B, et al. *Stroke.* 1999;30:917-923.
Indredavik B, et al. *Stroke.* 1997;28:1861-1866.
Indredavik B, et al. *Stroke.* 2000;31:2989-2994.

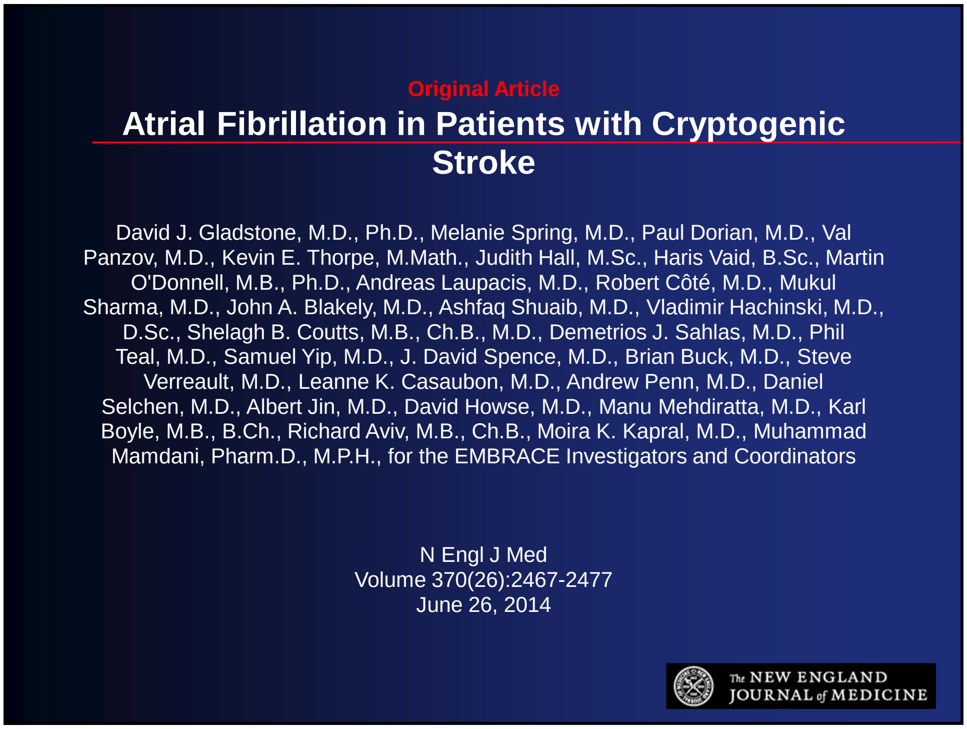
Goldstein LB, et al. *Neurology.* 2003;61:792-796.
Alberts MJ, et al. *JAMA.* 2000;283:3102-3109.
Gillum LA, et al. *Stroke.* 2001;32:2137-2142.



Work-up of TIA and Ischemic Stroke

All Patients
•Brain Imaging
•Neurovascular imaging
•Blood glucose
•Serum electrolytes
•CBC w/ Platelets
•PT/PTT/INR
•12 lead EKG/ROMI
•Holter monitoring
•TTE/TEE
•Supplemental O_2
•Fever reduction
•Lipids

Selected Patients
- Hepatic functions
- Toxicology
- Blood alcohol level
- Pregnancy
- Hypercoagulable w/u
- EEG
- LP



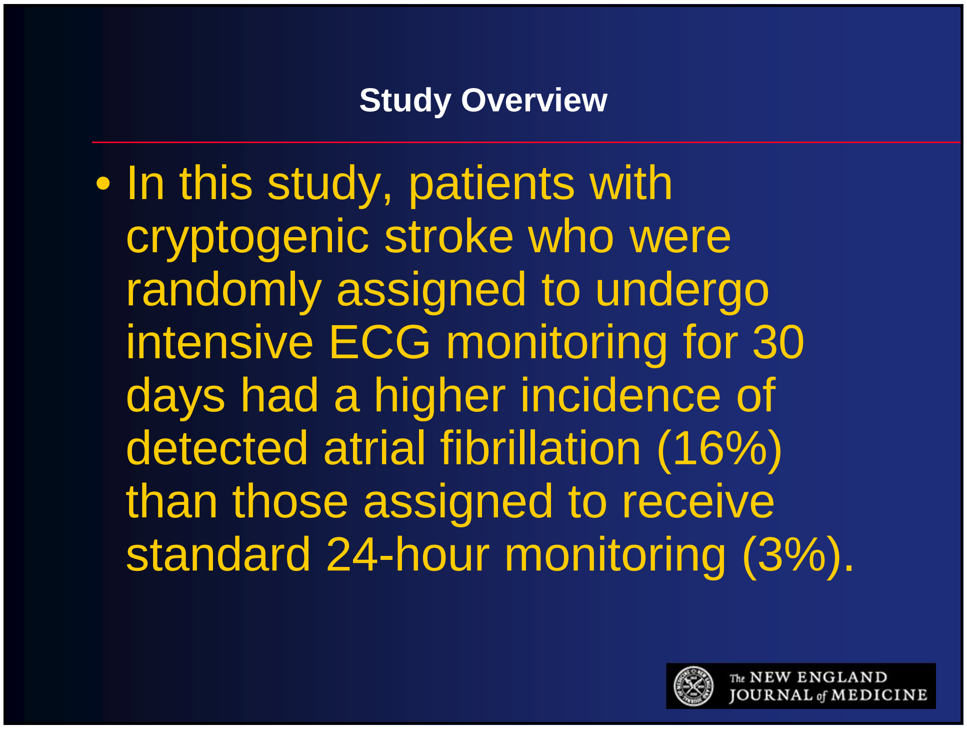
Original Article

Atrial Fibrillation in Patients with Cryptogenic Stroke

David J. Gladstone, M.D., Ph.D., Melanie Spring, M.D., Paul Dorian, M.D., Val Panzov, M.D., Kevin E. Thorpe, M.Math., Judith Hall, M.Sc., Haris Vaid, B.Sc., Martin O'Donnell, M.B., Ph.D., Andreas Laupacis, M.D., Robert Côté, M.D., Mukul Sharma, M.D., John A. Blakely, M.D., Ashfaq Shuaib, M.D., Vladimir Hachinski, M.D., D.Sc., Shelagh B. Coutts, M.B., Ch.B., M.D., Demetrios J. Sahlas, M.D., Phil Teal, M.D., Samuel Yip, M.D., J. David Spence, M.D., Brian Buck, M.D., Steve Verreault, M.D., Leanne K. Casaubon, M.D., Andrew Penn, M.D., Daniel Selchen, M.D., Albert Jin, M.D., David Howse, M.D., Manu Mehdiratta, M.D., Karl Boyle, M.B., B.Ch., Richard Aviv, M.B., Ch.B., Moira K. Kapral, M.D., Muhammad Mamdani, Pharm.D., M.P.H., for the EMBRACE Investigators and Coordinators

N Engl J Med
Volume 370(26):2467-2477
June 26, 2014

The NEW ENGLAND JOURNAL of MEDICINE



Study Overview

- In this study, patients with cryptogenic stroke who were randomly assigned to undergo intensive ECG monitoring for 30 days had a higher incidence of detected atrial fibrillation (16%) than those assigned to receive standard 24-hour monitoring (3%).

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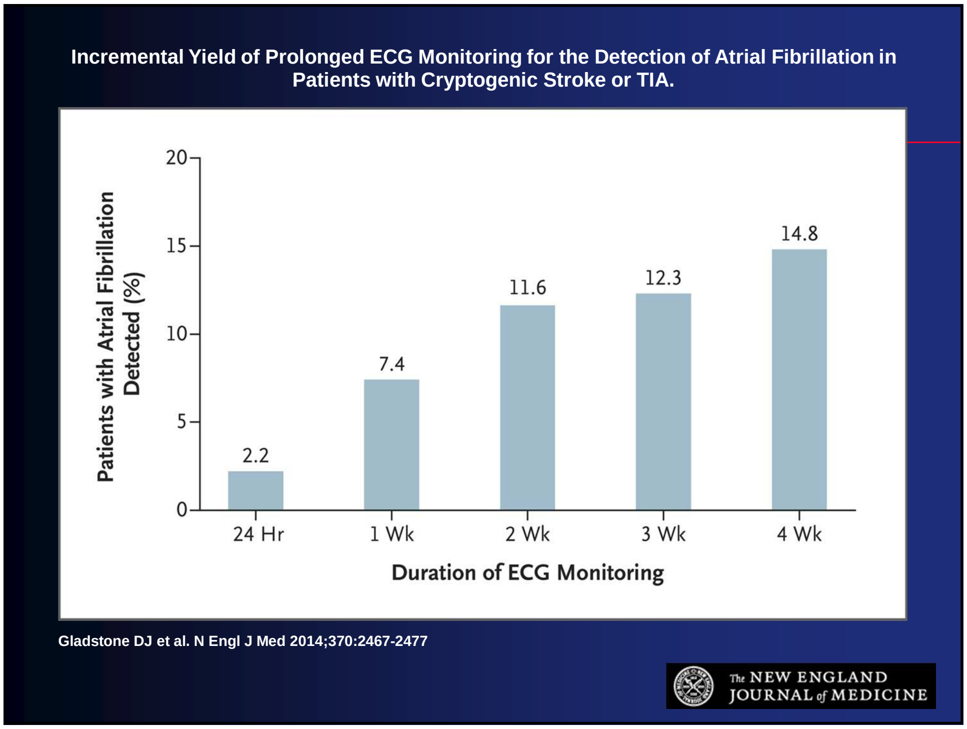

Incremental Yield of Prolonged ECG Monitoring for the Detection of Atrial Fibrillation in Patients with Cryptogenic Stroke or TIA.

Gladstone DJ et al. N Engl J Med 2014;370:2467-2477

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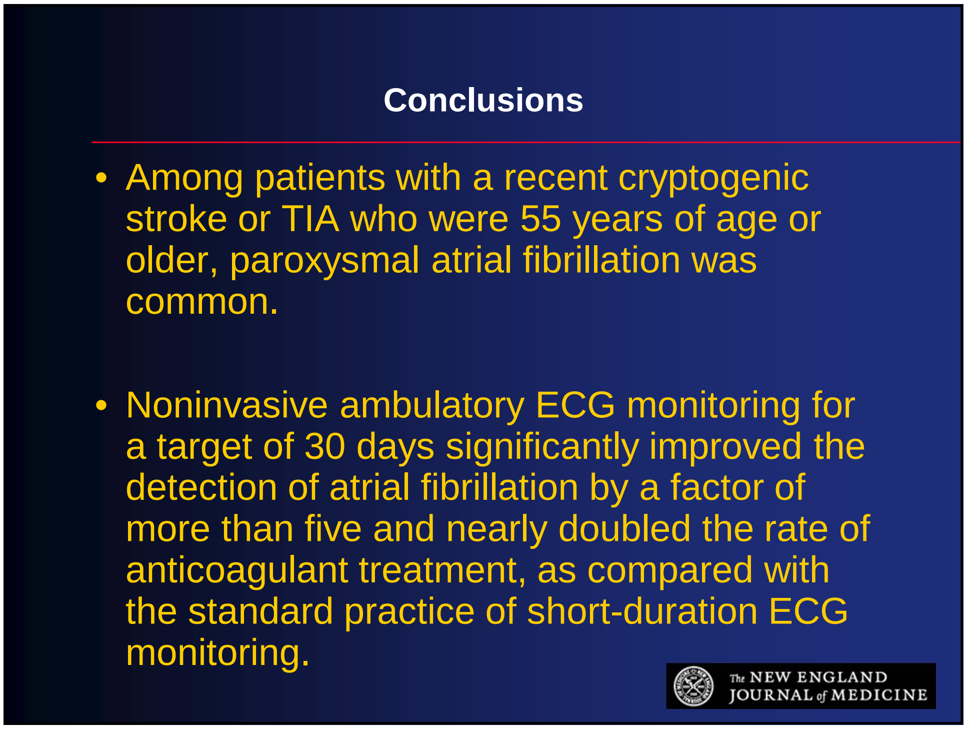

Conclusions

- Among patients with a recent cryptogenic stroke or TIA who were 55 years of age or older, paroxysmal atrial fibrillation was common.
- Noninvasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of atrial fibrillation by a factor of more than five and nearly doubled the rate of anticoagulant treatment, as compared with the standard practice of short-duration ECG monitoring.

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Discharged with:

- Blood pressure control
  - Diabetics ACEI/ARBs
- Antiplatelets
- Statins
- Lifestyle changes

Controversial or Investigational Secondary-Prevention Strategies

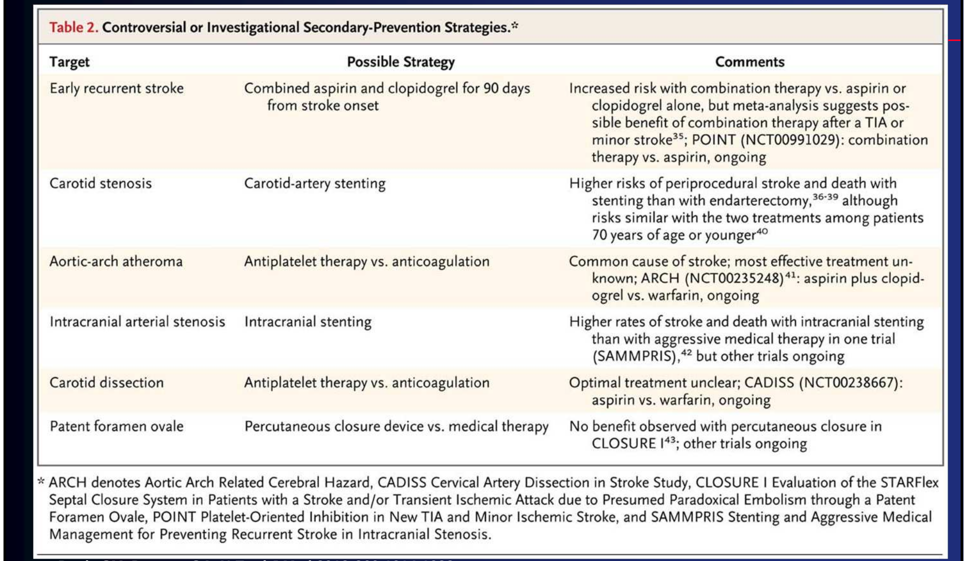
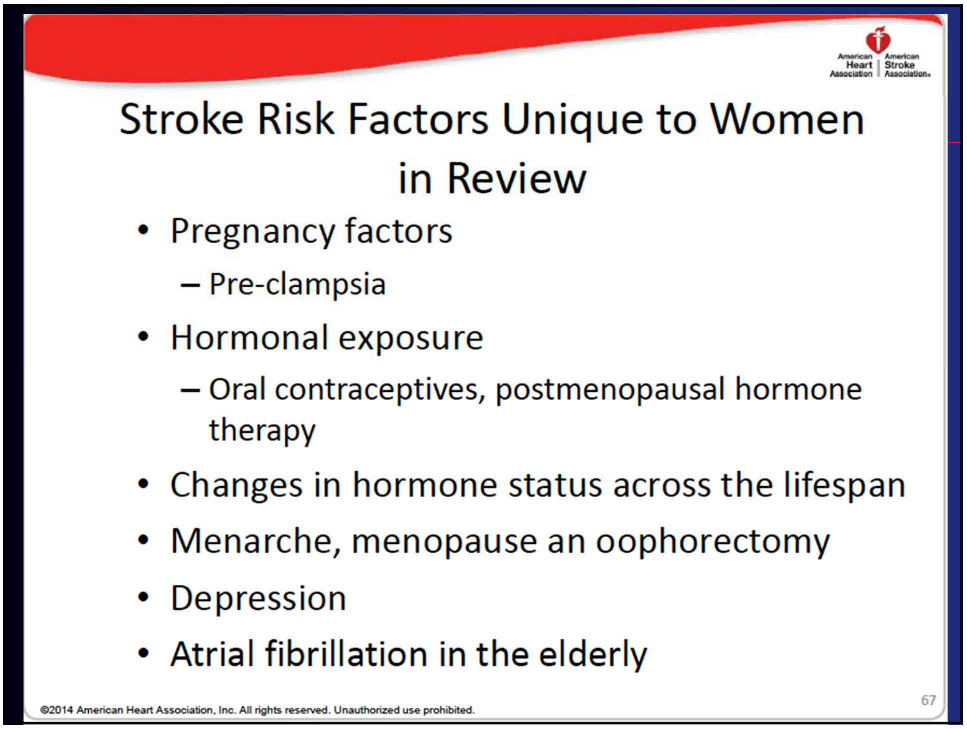


Table 2. Controversial or Investigational Secondary-Prevention Strategies.*

Target	Possible Strategy	Comments
Early recurrent stroke	Combined aspirin and clopidogrel for 90 days from stroke onset	Increased risk with combination therapy vs. aspirin or clopidogrel alone, but meta-analysis suggests possible benefit of combination therapy after a TIA or minor stroke[35]; POINT (NCT00991029): combination therapy vs. aspirin, ongoing
Carotid stenosis	Carotid-artery stenting	Higher risks of periprocedural stroke and death with stenting than with endarterectomy,[36-39] although risks similar with the two treatments among patients 70 years of age or younger[40]
Aortic-arch atheroma	Antiplatelet therapy vs. anticoagulation	Common cause of stroke; most effective treatment unknown; ARCH (NCT00235248)[41]: aspirin plus clopidogrel vs. warfarin, ongoing
Intracranial arterial stenosis	Intracranial stenting	Higher rates of stroke and death with intracranial stenting than with aggressive medical therapy in one trial (SAMMPRIS),[42] but other trials ongoing
Carotid dissection	Antiplatelet therapy vs. anticoagulation	Optimal treatment unclear; CADISS (NCT00238667): aspirin vs. warfarin, ongoing
Patent foramen ovale	Percutaneous closure device vs. medical therapy	No benefit observed with percutaneous closure in CLOSURE I[43]; other trials ongoing

* ARCH denotes Aortic Arch Related Cerebral Hazard, CADISS Cervical Artery Dissection in Stroke Study, CLOSURE I Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale, POINT Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke, and SAMMPRIS Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis.

Davis SM, Donnan GA. N Engl J Med 2012;366:1914-1922



Stroke Risk Factors Unique to Women in Review

- Pregnancy factors
  - Pre-clampsia
- Hormonal exposure
  - Oral contraceptives, postmenopausal hormone therapy
- Changes in hormone status across the lifespan
- Menarche, menopause an oophorectomy
- Depression
- Atrial fibrillation in the elderly

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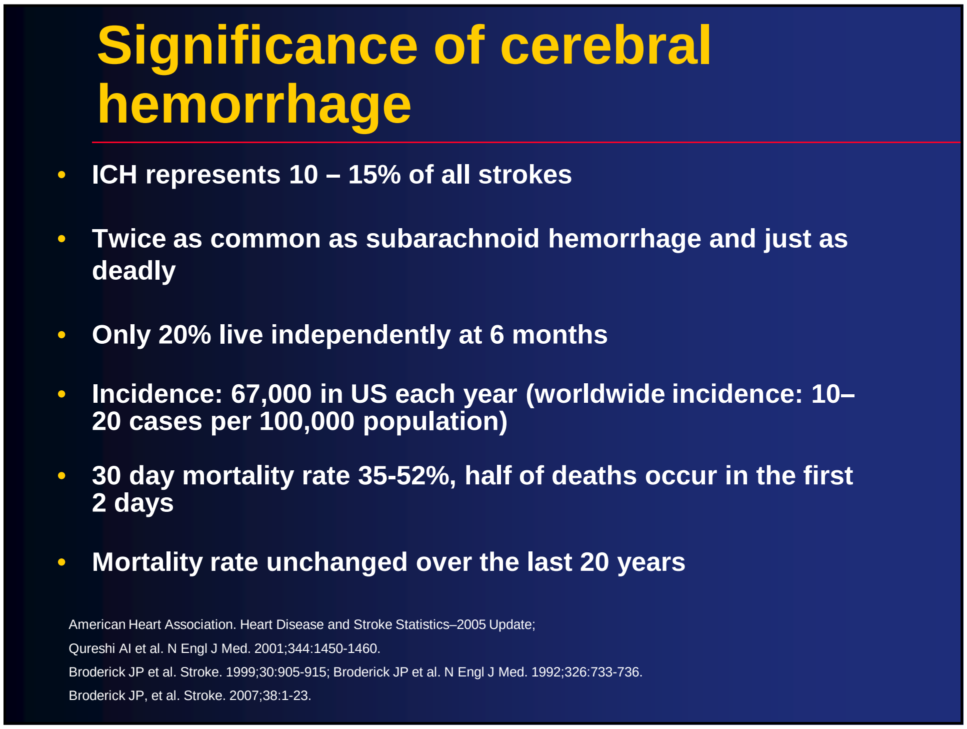
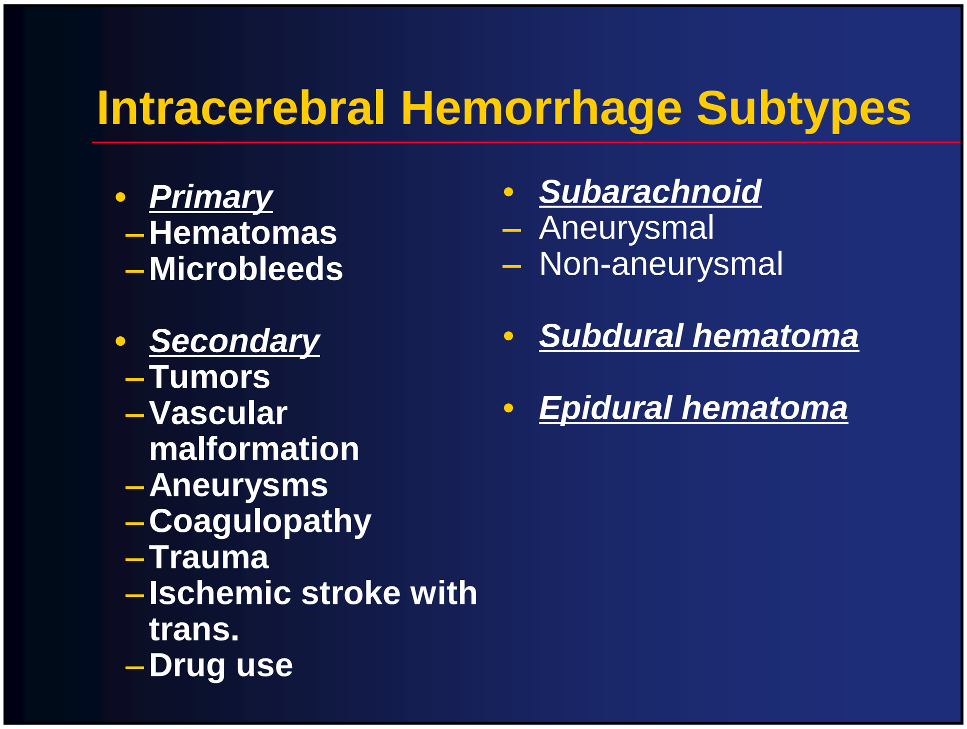


Significance of cerebral hemorrhage

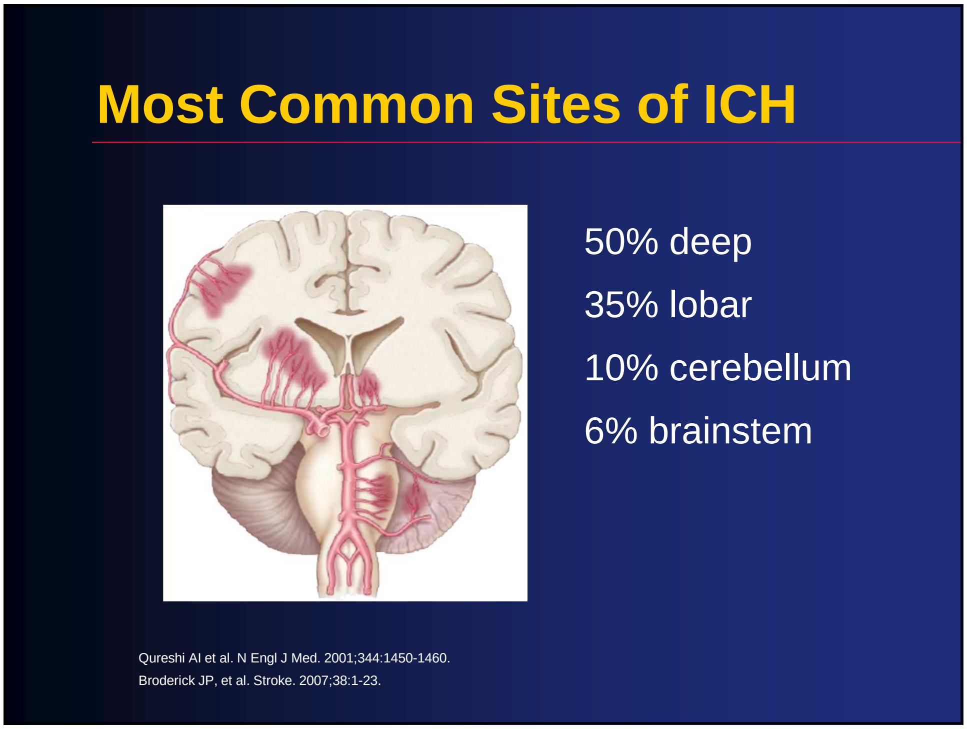
- ICH represents 10 – 15% of all strokes
- Twice as common as subarachnoid hemorrhage and just as deadly
- Only 20% live independently at 6 months
- Incidence: 67,000 in US each year (worldwide incidence: 10–20 cases per 100,000 population)
- 30 day mortality rate 35-52%, half of deaths occur in the first 2 days
- Mortality rate unchanged over the last 20 years

American Heart Association. Heart Disease and Stroke Statistics–2005 Update;
Qureshi AI et al. N Engl J Med. 2001;344:1450-1460.
Broderick JP et al. Stroke. 1999;30:905-915; Broderick JP et al. N Engl J Med. 1992;326:733-736.
Broderick JP, et al. Stroke. 2007;38:1-23.



Intracerebral Hemorrhage Subtypes

- ***Primary***
  - Hematomas
  - Microbleeds
- ***Secondary***
  - Tumors
  - Vascular malformation
  - Aneurysms
  - Coagulopathy
  - Trauma
  - Ischemic stroke with trans.
  - Drug use
- ***Subarachnoid***
  - Aneurysmal
  - Non-aneurysmal
- ***Subdural hematoma***
- ***Epidural hematoma***



Most Common Sites of ICH

50% deep

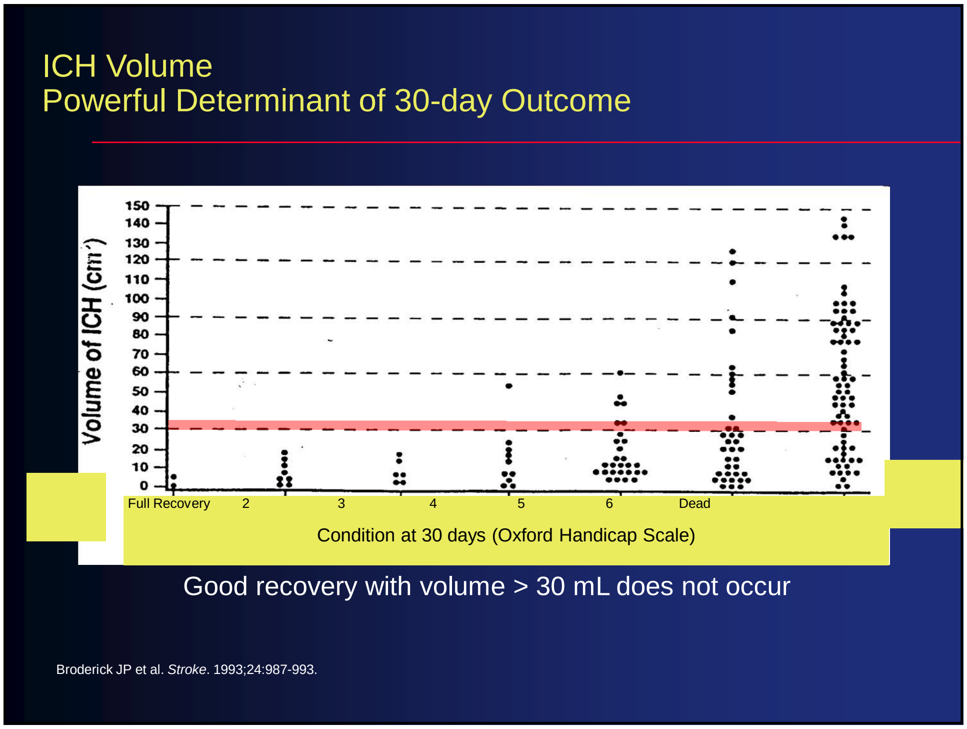
35% lobar

10% cerebellum

6% brainstem

Qureshi AI et al. N Engl J Med. 2001;344:1450-1460.

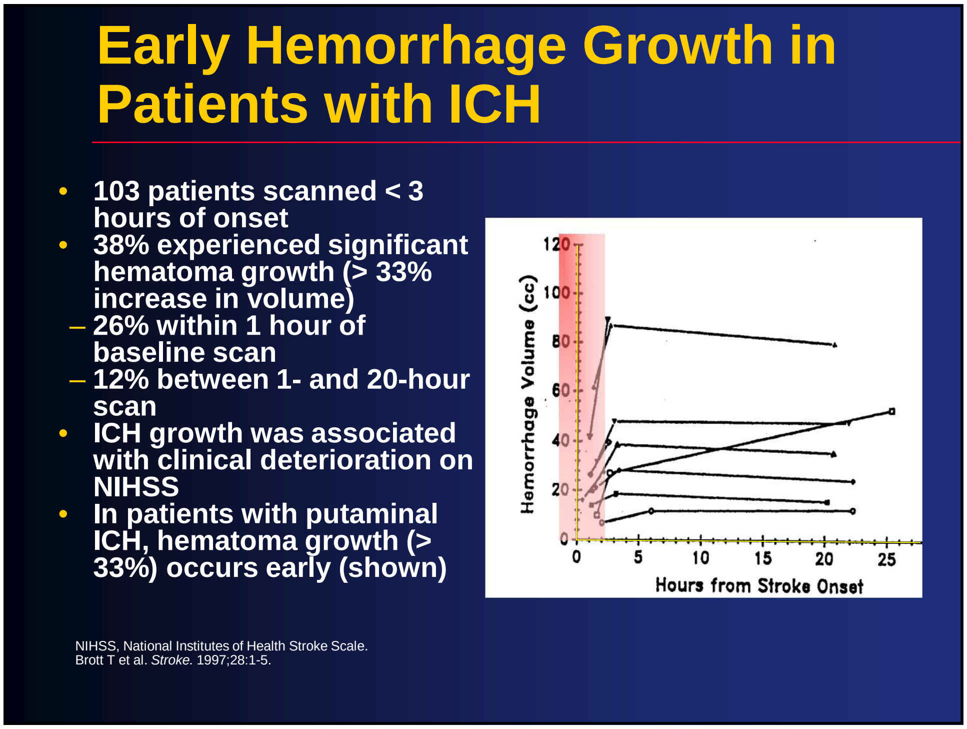
Broderick JP, et al. Stroke. 2007;38:1-23.



ICH Volume
Powerful Determinant of 30-day Outcome

Good recovery with volume > 30 mL does not occur

Broderick JP et al. *Stroke*. 1993;24:987-993.



Early Hemorrhage Growth in Patients with ICH

- **103 patients scanned < 3 hours of onset**
- **38% experienced significant hematoma growth (> 33% increase in volume)**
  - **26% within 1 hour of baseline scan**
  - **12% between 1- and 20-hour scan**
- **ICH growth was associated with clinical deterioration on NIHSS**
- **In patients with putaminal ICH, hematoma growth (> 33%) occurs early (shown)**

NIHSS, National Institutes of Health Stroke Scale.
Brott T et al. *Stroke.* 1997;28:1-5.

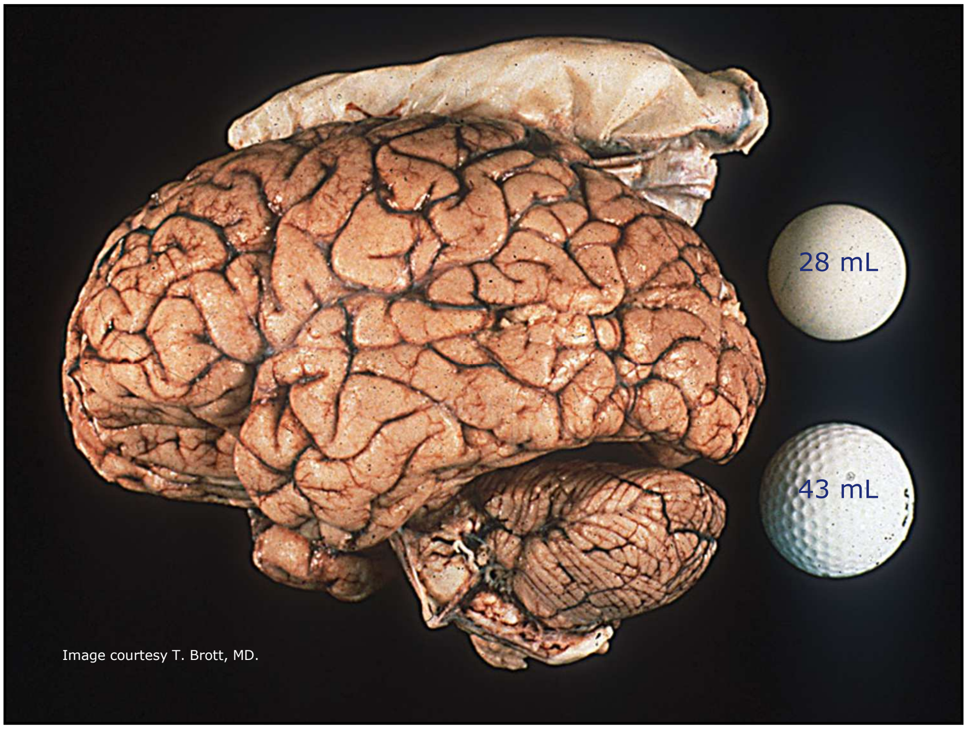
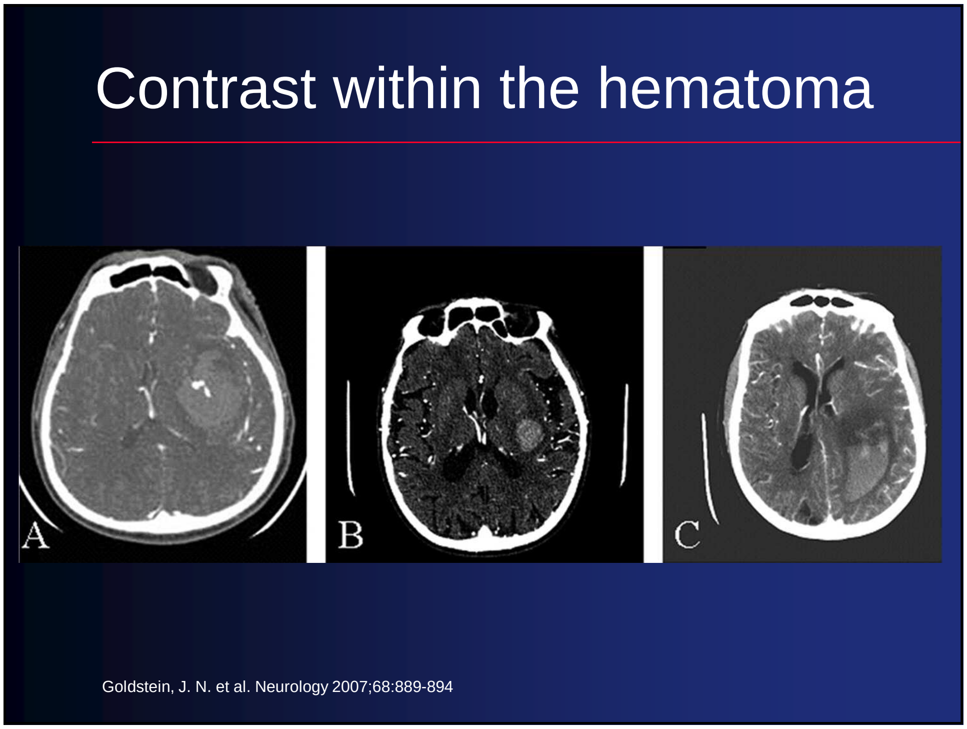
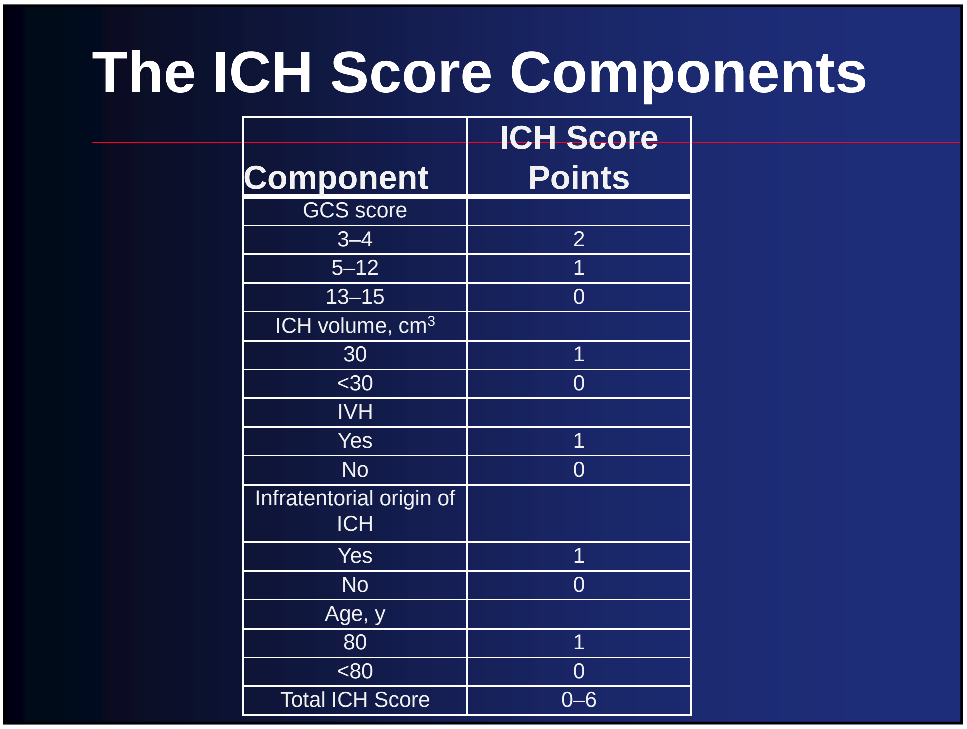


Image courtesy T. Brott, MD.



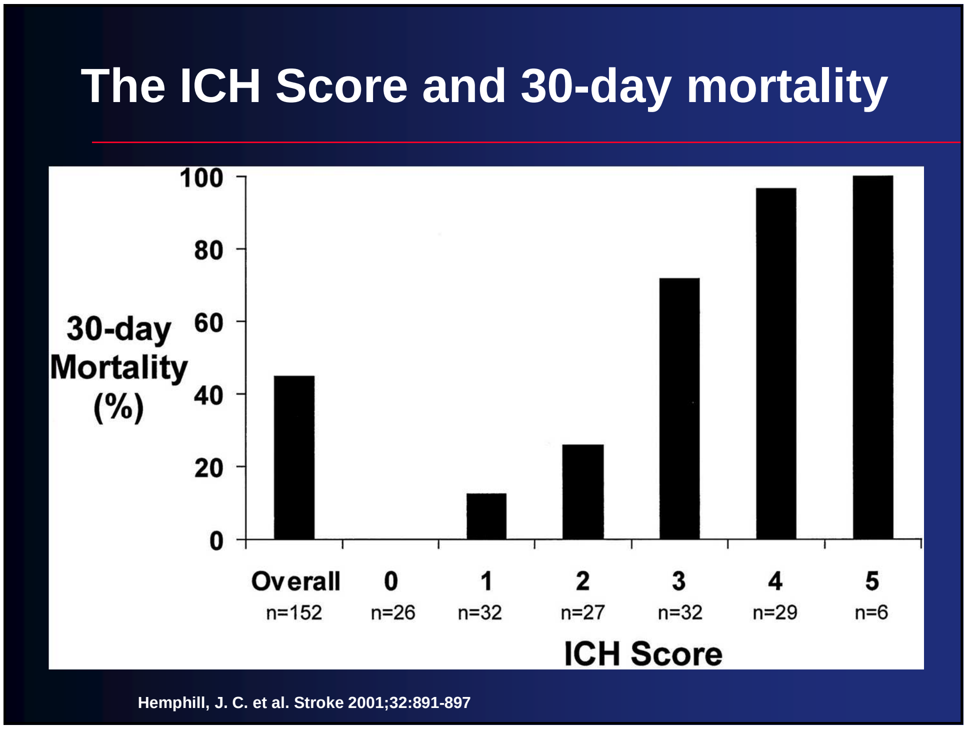
Contrast within the hematoma

Goldstein, J. N. et al. Neurology 2007;68:889-894



The ICH Score Components

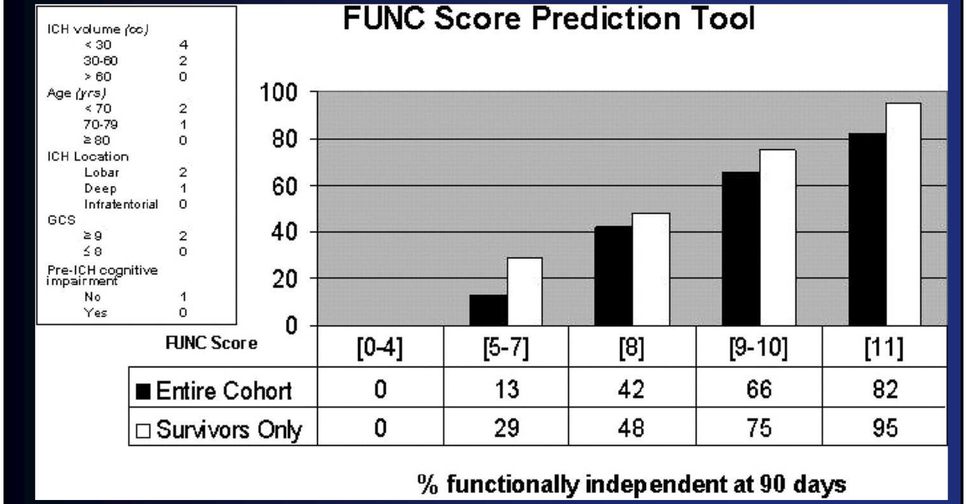
Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
80	1
<80	0
Total ICH Score	0–6



The ICH Score and 30-day mortality

Hemphill, J. C. et al. Stroke 2001;32:891-897

FUNC score prediction tool



FUNC Score Prediction Tool

ICH volume (cc)	
< 30	4
30-60	2
> 60	0
Age (yrs)	
< 70	2
70-79	1
≥ 80	0
ICH Location	
Lobar	2
Deep	1
Infratentorial	0
GCS	
≥ 9	2
≤ 8	0
Pre-ICH cognitive impairment	
No	1
Yes	0

FUNC Score	[0-4]	[5-7]	[8]	[9-10]	[11]
■ Entire Cohort	0	13	42	66	82
☐ Survivors Only	0	29	48	75	95

% functionally independent at 90 days

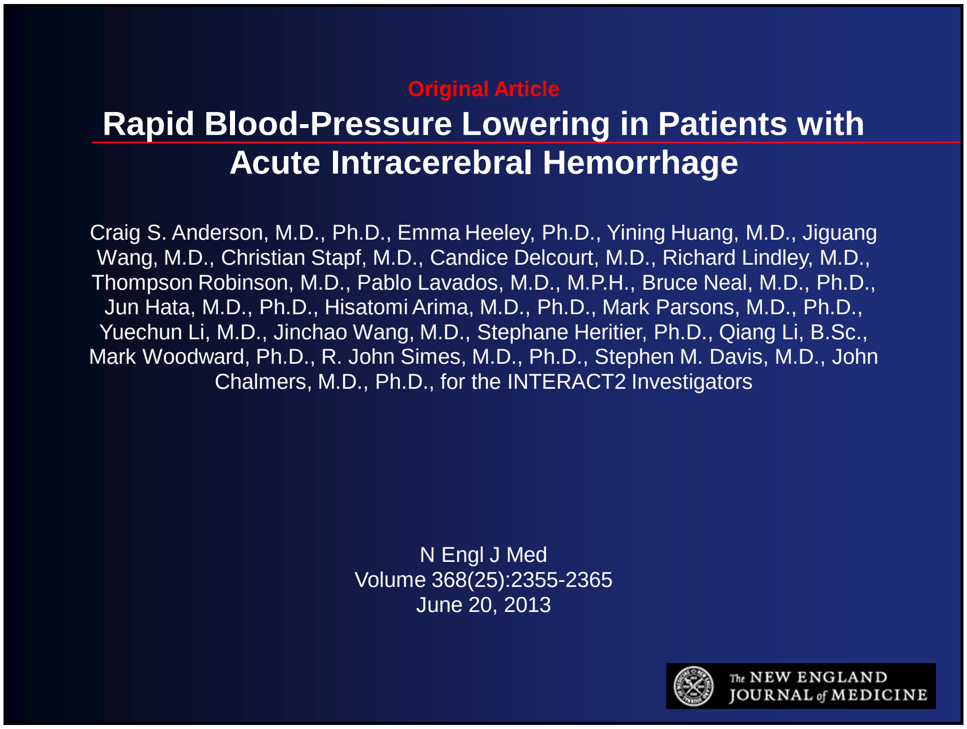
Rost, N. S. et al. Stroke 2008;39:2304-2309

AHA Treatment Guidelines for ICH

BP level (mm Hg)	Treatment to Consider
SBP > 200 or MAP > 150	**Aggressive reduction of blood pressure with continuous intravenous infusion**
SBP > 180 or MAP > 130 and evidence or suspicion of elevated ICP	**Monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep CPP > 60-80 mm Hg**
SBP > 180 or MAP > 130 and no evidence or suspicion or elevated ICP	**Modest reduction of blood pressure (eg. MAP of 110 or target blood of 160/90 mm Hg) using intermittent or continuous intravenous**

AHA = American Heart Association; ICH = intracerebral hemorrhage; SBP = systolic blood pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure; ICP = intracranial pressure

Broderick JP, et al. *Stroke*. 2007;38:1-23.

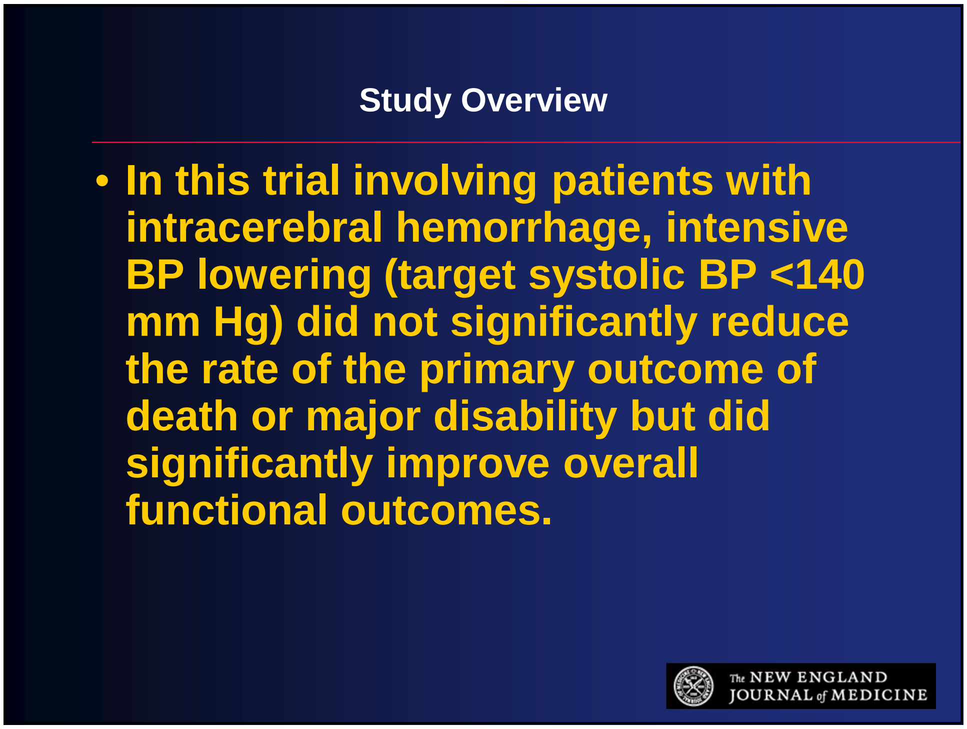


Original Article

Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

Craig S. Anderson, M.D., Ph.D., Emma Heeley, Ph.D., Yining Huang, M.D., Jiguang Wang, M.D., Christian Stapf, M.D., Candice Delcourt, M.D., Richard Lindley, M.D., Thompson Robinson, M.D., Pablo Lavados, M.D., M.P.H., Bruce Neal, M.D., Ph.D., Jun Hata, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Mark Parsons, M.D., Ph.D., Yuechun Li, M.D., Jinchao Wang, M.D., Stephane Heritier, Ph.D., Qiang Li, B.Sc., Mark Woodward, Ph.D., R. John Simes, M.D., Ph.D., Stephen M. Davis, M.D., John Chalmers, M.D., Ph.D., for the INTERACT2 Investigators

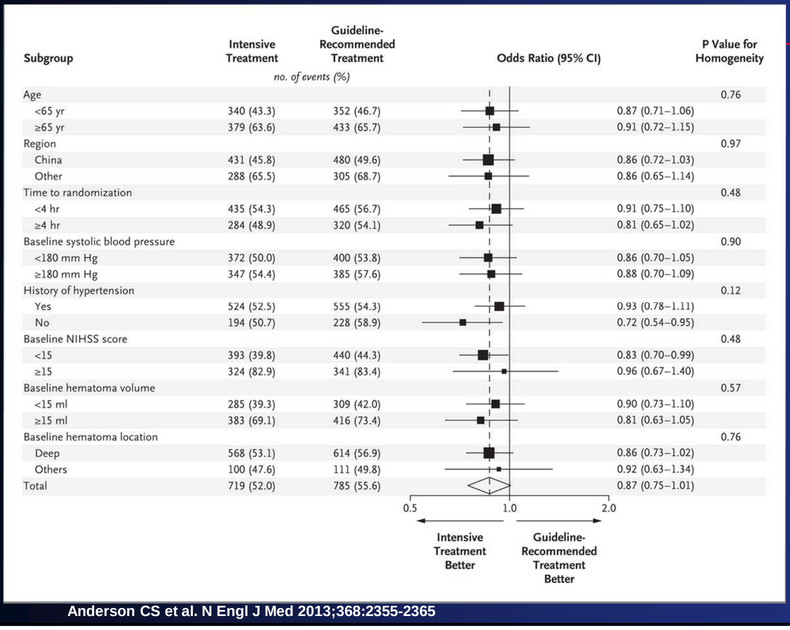
N Engl J Med
Volume 368(25):2355-2365
June 20, 2013



Study Overview

- In this trial involving patients with intracerebral hemorrhage, intensive BP lowering (target systolic BP <140 mm Hg) did not significantly reduce the rate of the primary outcome of death or major disability but did significantly improve overall functional outcomes.

Effect of Early Intensive Blood-Pressure–Lowering Treatment on the Primary Outcome, According to Prespecified Subgroups.



Subgroup	Intensive Treatment	Guideline-Recommended Treatment	Odds Ratio (95% CI)	P Value for Homogeneity
	no. of events (%)			
Age				0.76
<65 yr	340 (43.3)	352 (46.7)	0.87 (0.71–1.06)	
≥65 yr	379 (63.6)	433 (65.7)	0.91 (0.72–1.15)	
Region				0.97
China	431 (45.8)	480 (49.6)	0.86 (0.72–1.03)	
Other	288 (65.5)	305 (68.7)	0.86 (0.65–1.14)	
Time to randomization				0.48
<4 hr	435 (54.3)	465 (56.7)	0.91 (0.75–1.10)	
≥4 hr	284 (48.9)	320 (54.1)	0.81 (0.65–1.02)	
Baseline systolic blood pressure				0.90
<180 mm Hg	372 (50.0)	400 (53.8)	0.86 (0.70–1.05)	
≥180 mm Hg	347 (54.4)	385 (57.6)	0.88 (0.70–1.09)	
History of hypertension				0.12
Yes	524 (52.5)	555 (54.3)	0.93 (0.78–1.11)	
No	194 (50.7)	228 (58.9)	0.72 (0.54–0.95)	
Baseline NIHSS score				0.48
<15	393 (39.8)	440 (44.3)	0.83 (0.70–0.99)	
≥15	324 (82.9)	341 (83.4)	0.96 (0.67–1.40)	
Baseline hematoma volume				0.57
<15 ml	285 (39.3)	309 (42.0)	0.90 (0.73–1.10)	
≥15 ml	383 (69.1)	416 (73.4)	0.81 (0.63–1.05)	
Baseline hematoma location				0.76
Deep	568 (53.1)	614 (56.9)	0.86 (0.73–1.02)	
Others	100 (47.6)	111 (49.8)	0.92 (0.63–1.34)	
Total	719 (52.0)	785 (55.6)	0.87 (0.75–1.01)	

0.5
1.0
2.0
Intensive Treatment Better
Guideline-Recommended Treatment Better

Anderson CS et al. N Engl J Med 2013;368:2355-2365

Conclusions

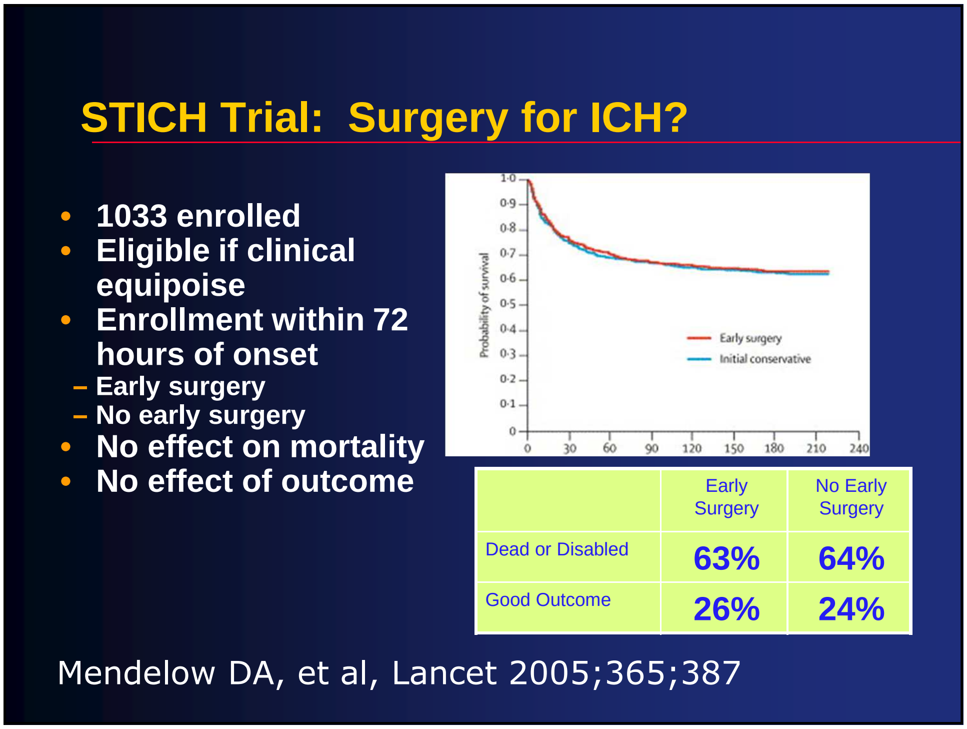
- In patients with intracerebral hemorrhage, intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or severe disability.
- An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of blood pressure.

The NEW ENGLAND JOURNAL of MEDICINE

Surgical Therapies for ICH

- Surgical evacuation
  - Large (>3 cm) cerebellar hemorrhages
  - Large lobular hemorrhages
  - Substantial mass effect
  - Rapidly deteriorating condition

O’Connell KA, et al. *JAMA.* 2006;295:293-298.

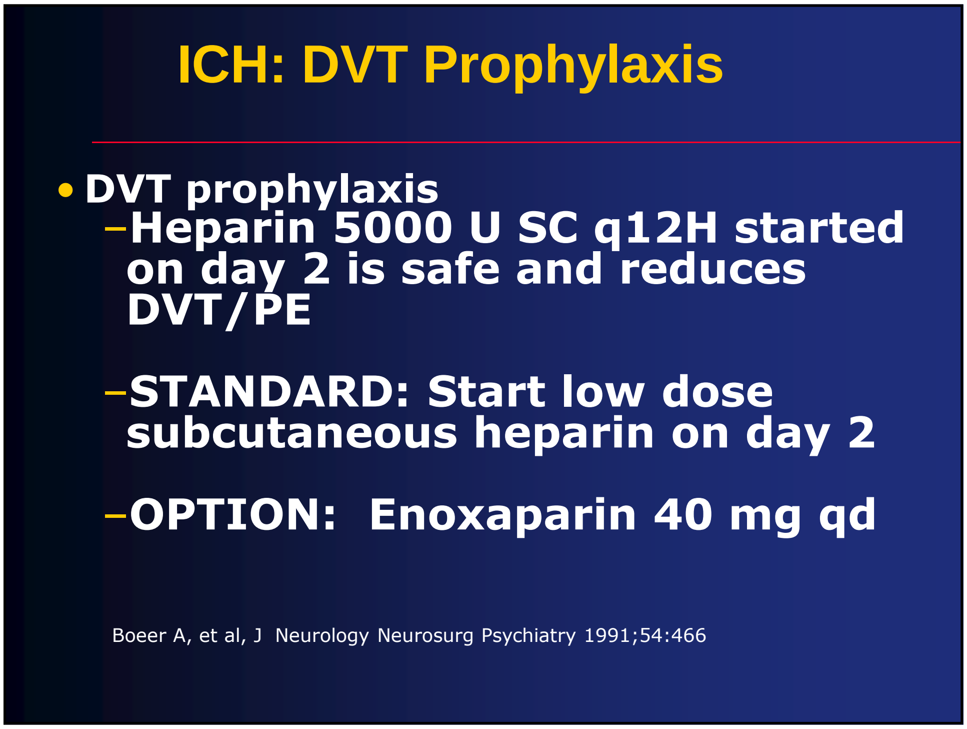


STICH Trial: Surgery for ICH?

- 1033 enrolled
- Eligible if clinical equipoise
- Enrollment within 72 hours of onset
  - Early surgery
  - No early surgery
- No effect on mortality
- No effect of outcome

	Early Surgery	No Early Surgery
Dead or Disabled	63%	64%
Good Outcome	26%	24%

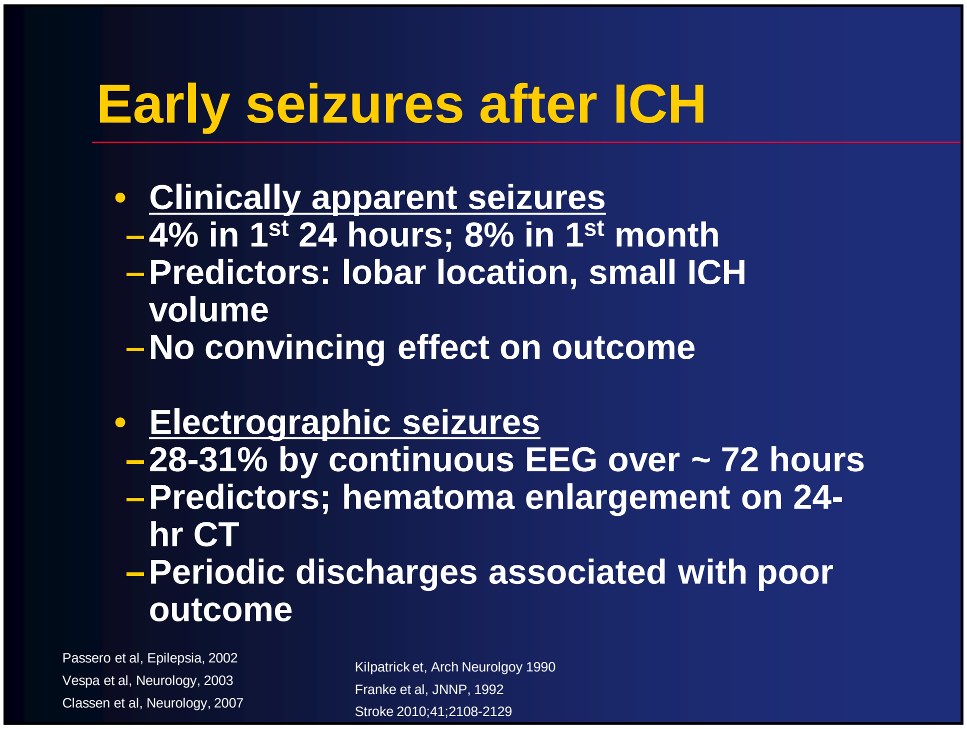
Mendelow DA, et al, Lancet 2005;365;387



ICH: DVT Prophylaxis

- DVT prophylaxis
  - Heparin 5000 U SC q12H started on day 2 is safe and reduces DVT/PE
  - STANDARD: Start low dose subcutaneous heparin on day 2
  - OPTION: Enoxaparin 40 mg qd

Boeer A, et al, J Neurology Neurosurg Psychiatry 1991;54:466

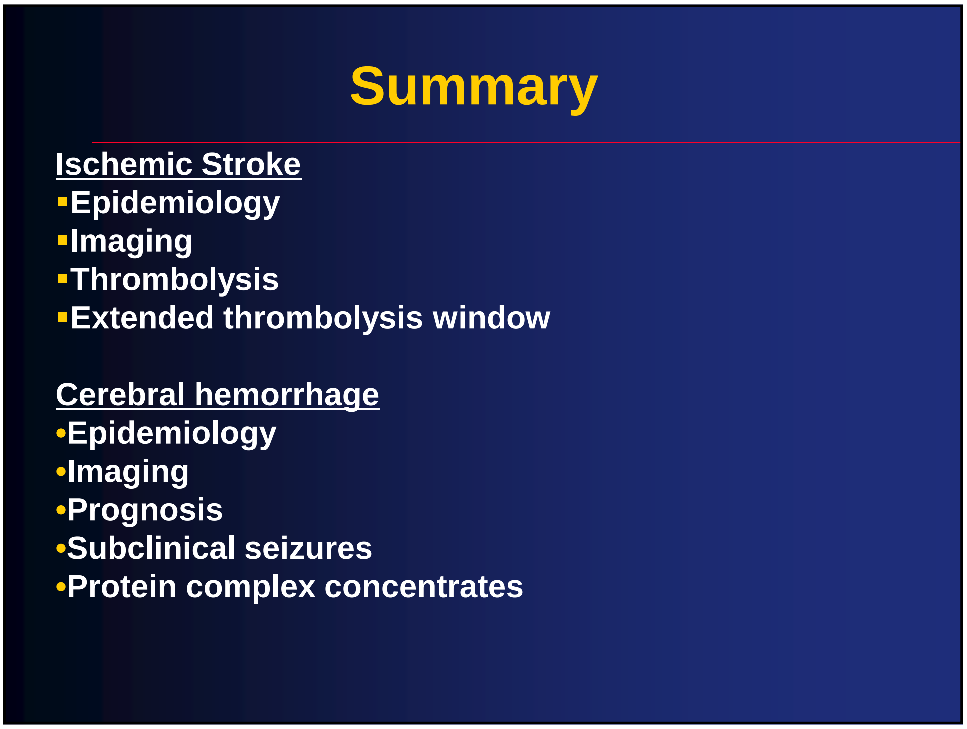


Early seizures after ICH

- Clinically apparent seizures
  - 4% in 1st 24 hours; 8% in 1st month
  - Predictors: lobar location, small ICH volume
  - No convincing effect on outcome
- Electrographic seizures
  - 28-31% by continuous EEG over ~ 72 hours
  - Predictors; hematoma enlargement on 24-hr CT
  - Periodic discharges associated with poor outcome

Passero et al, Epilepsia, 2002
Vespa et al, Neurology, 2003
Classen et al, Neurology, 2007

Kilpatrick et, Arch Neurolgoy 1990
Franke et al, JNNP, 1992
Stroke 2010;41;2108-2129



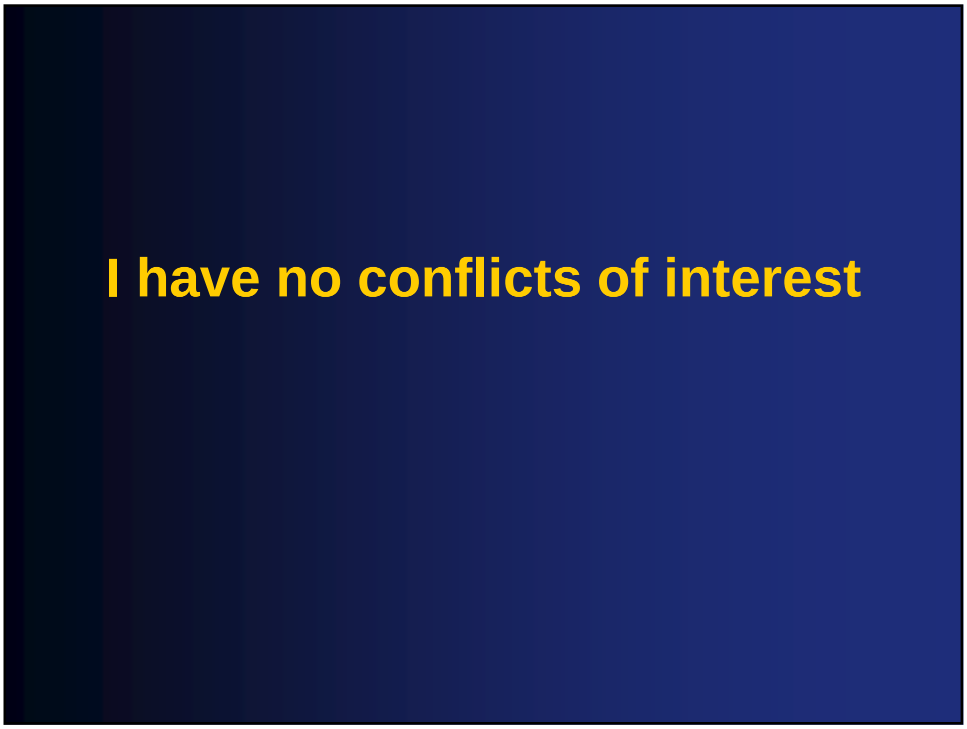
Summary

Ischemic Stroke

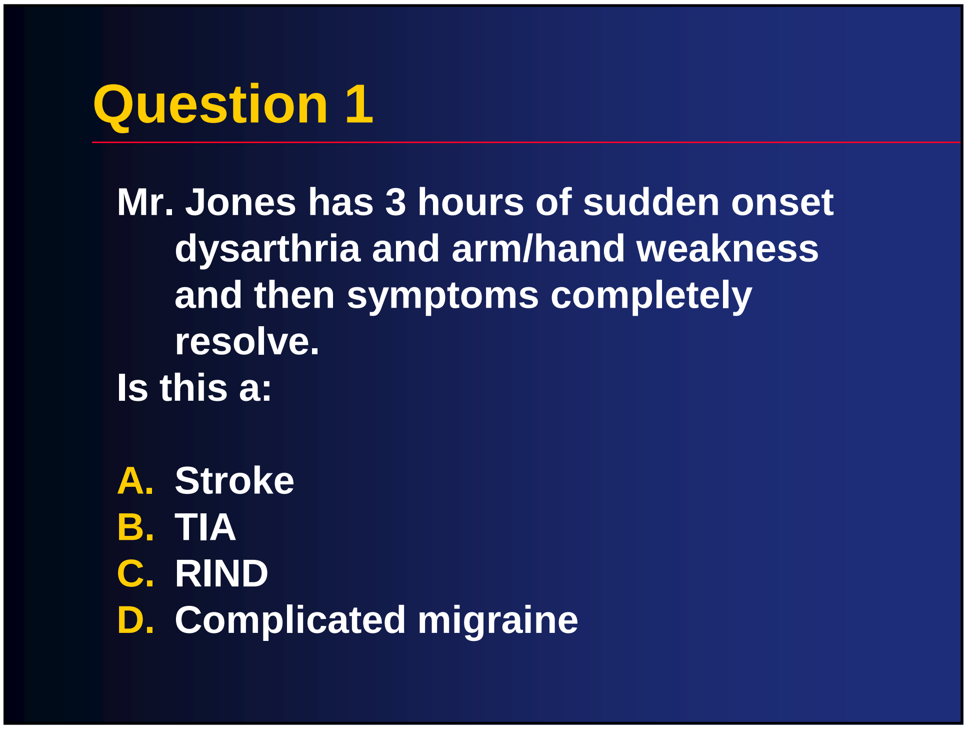
- Epidemiology
- Imaging
- Thrombolysis
- Extended thrombolysis window

Cerebral hemorrhage

- Epidemiology
- Imaging
- Prognosis
- Subclinical seizures
- Protein complex concentrates



I have no conflicts of interest

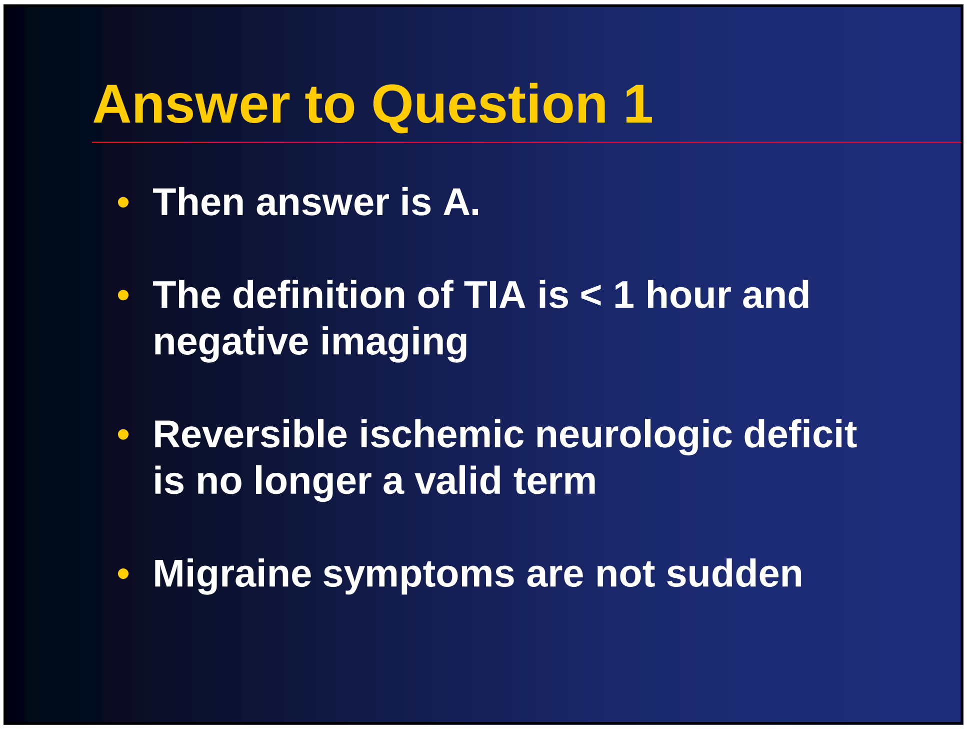


Question 1

Mr. Jones has 3 hours of sudden onset dysarthria and arm/hand weakness and then symptoms completely resolve.

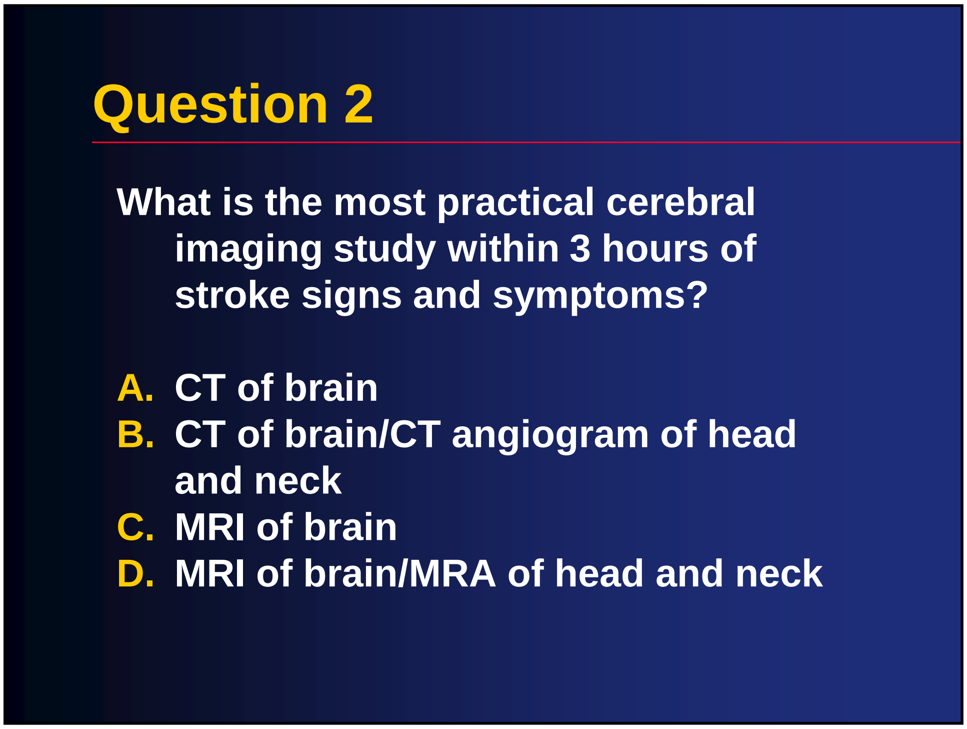
Is this a:

A. Stroke
B. TIA
C. RIND
D. Complicated migraine



Answer to Question 1

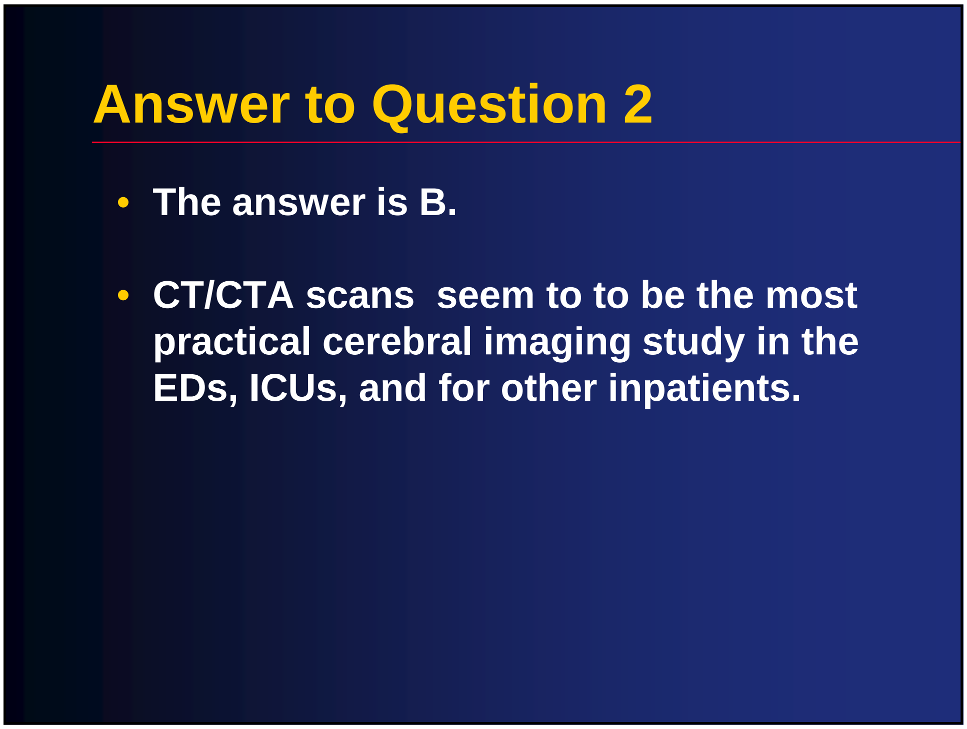
- Then answer is A.
- The definition of TIA is < 1 hour and negative imaging
- Reversible ischemic neurologic deficit is no longer a valid term
- Migraine symptoms are not sudden



Question 2

What is the most practical cerebral imaging study within 3 hours of stroke signs and symptoms?

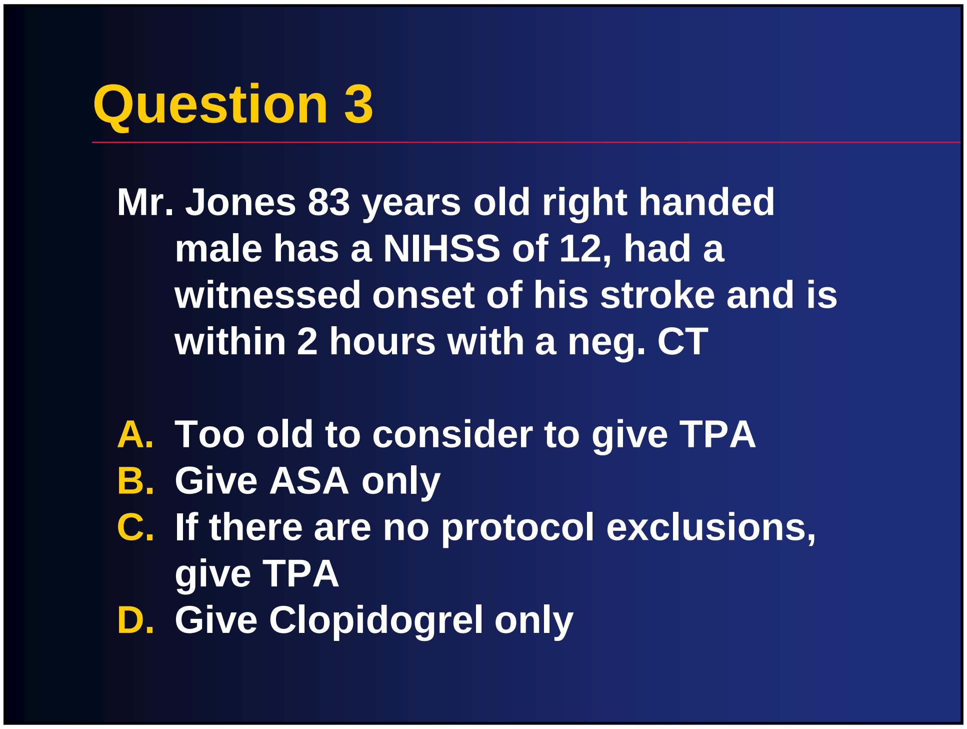
A. CT of brain
B. CT of brain/CT angiogram of head and neck
C. MRI of brain
D. MRI of brain/MRA of head and neck



Answer to Question 2

- The answer is B.

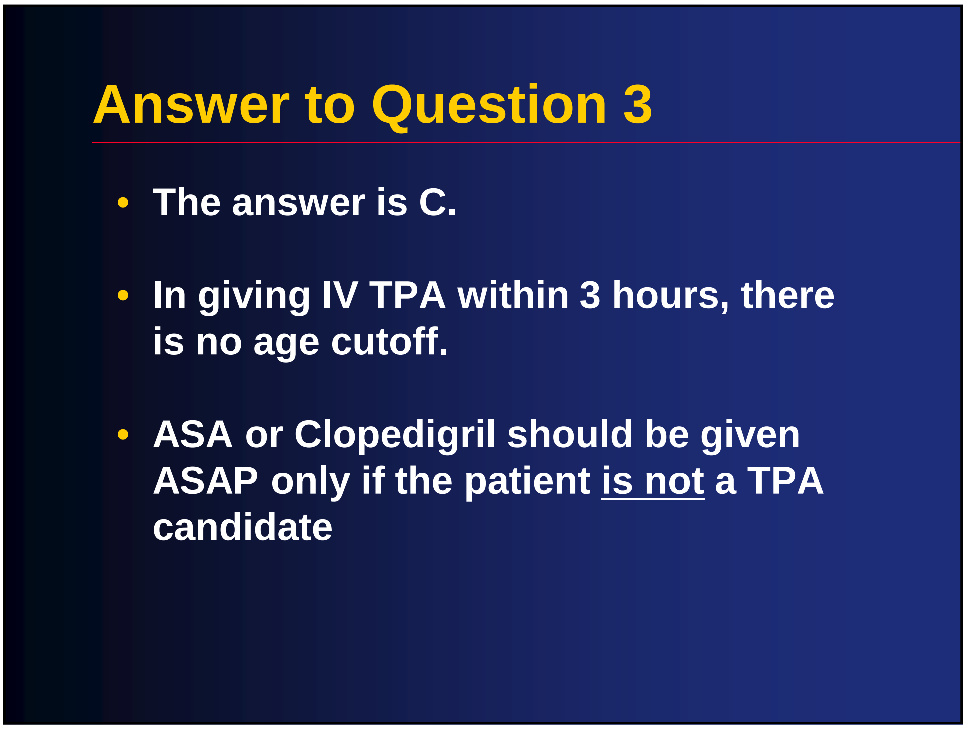
- CT/CTA scans seem to to be the most practical cerebral imaging study in the EDs, ICUs, and for other inpatients.



Question 3

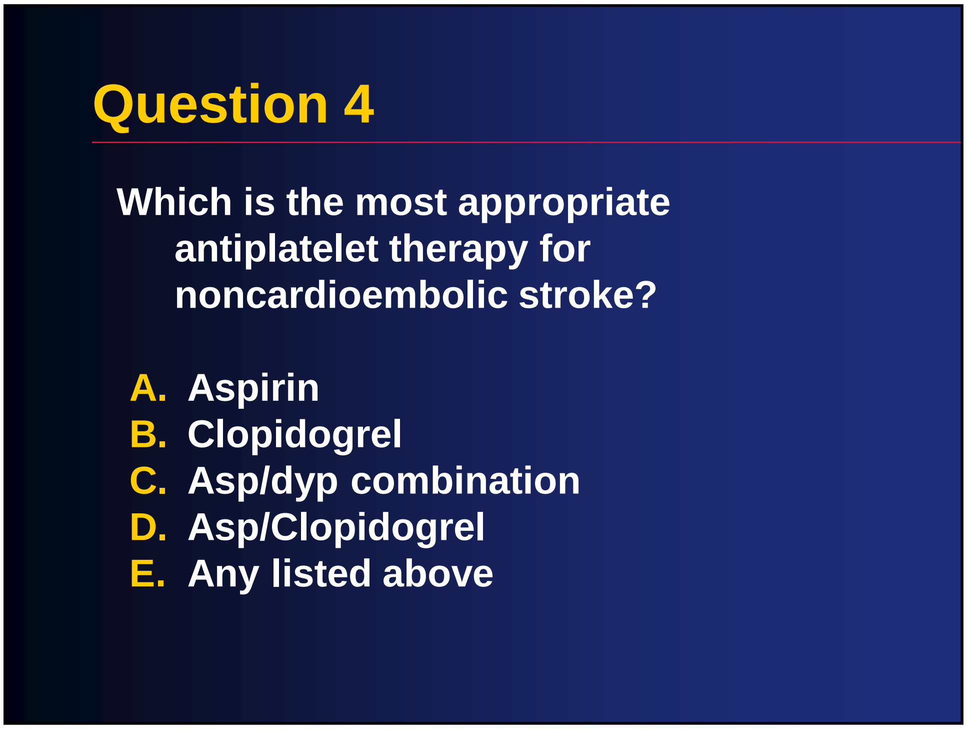
Mr. Jones 83 years old right handed male has a NIHSS of 12, had a witnessed onset of his stroke and is within 2 hours with a neg. CT

A. Too old to consider to give TPA
B. Give ASA only
C. If there are no protocol exclusions, give TPA
D. Give Clopidogrel only



Answer to Question 3

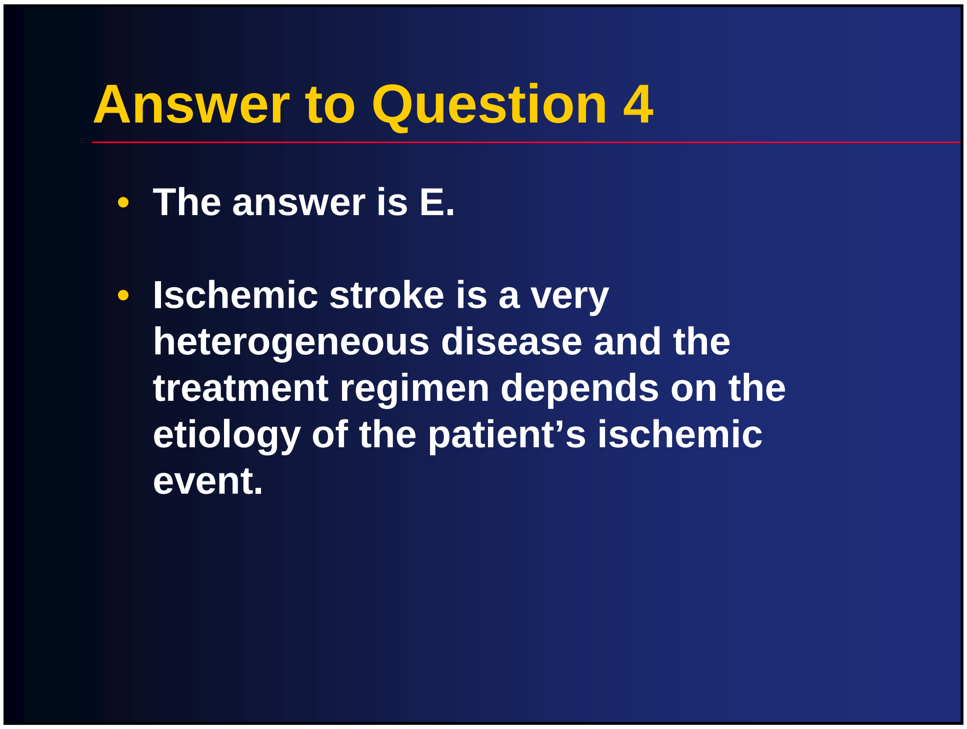
- The answer is C.
- In giving IV TPA within 3 hours, there is no age cutoff.
- ASA or Clopedigril should be given ASAP only if the patient is not a TPA candidate



Question 4

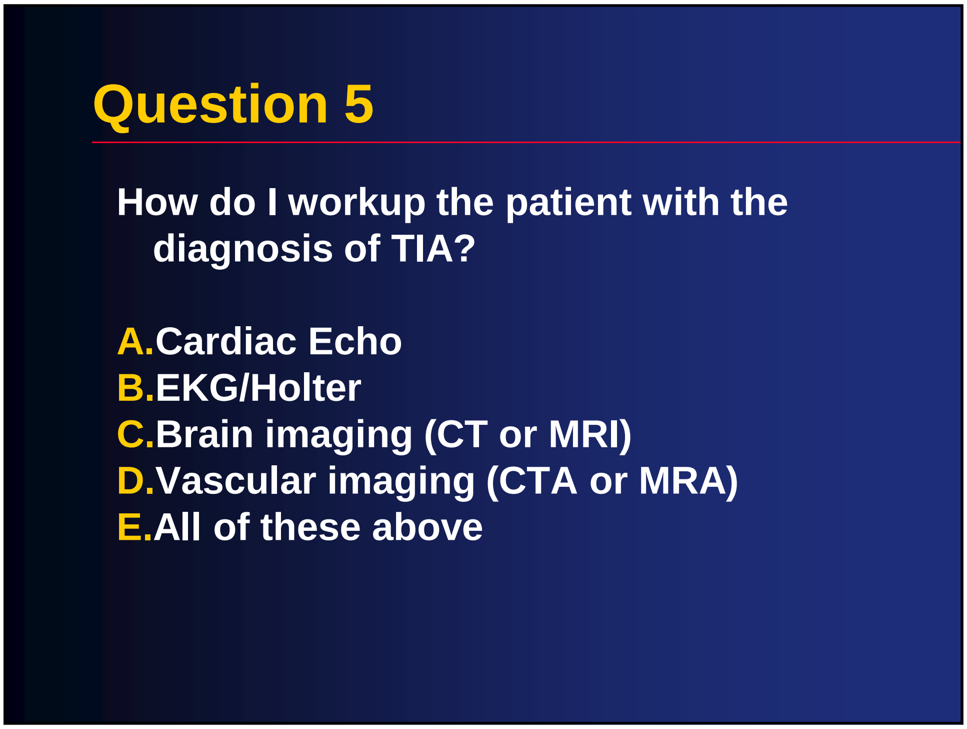
Which is the most appropriate antiplatelet therapy for noncardioembolic stroke?

A. Aspirin
B. Clopidogrel
C. Asp/dyp combination
D. Asp/Clopidogrel
E. Any listed above



Answer to Question 4

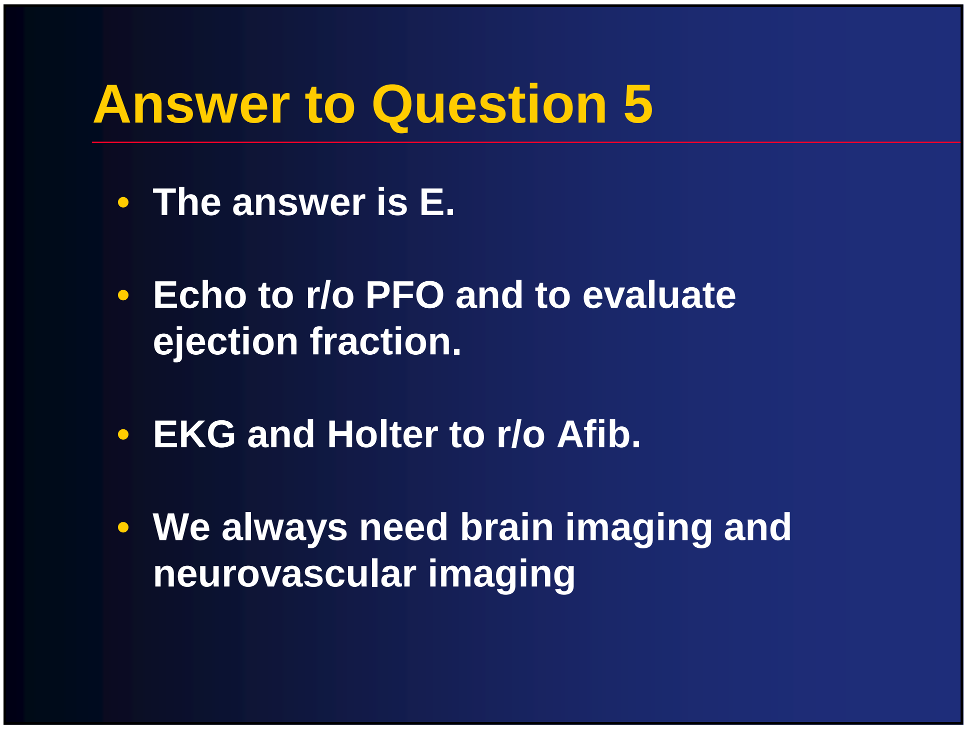
- The answer is E.
- Ischemic stroke is a very heterogeneous disease and the treatment regimen depends on the etiology of the patient’s ischemic event.



Question 5

How do I workup the patient with the diagnosis of TIA?

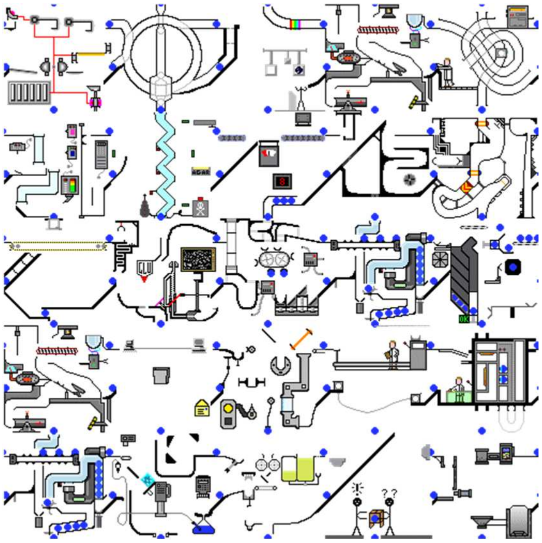
A. Cardiac Echo
B. EKG/Holter
C. Brain imaging (CT or MRI)
D. Vascular imaging (CTA or MRA)
E. All of these above

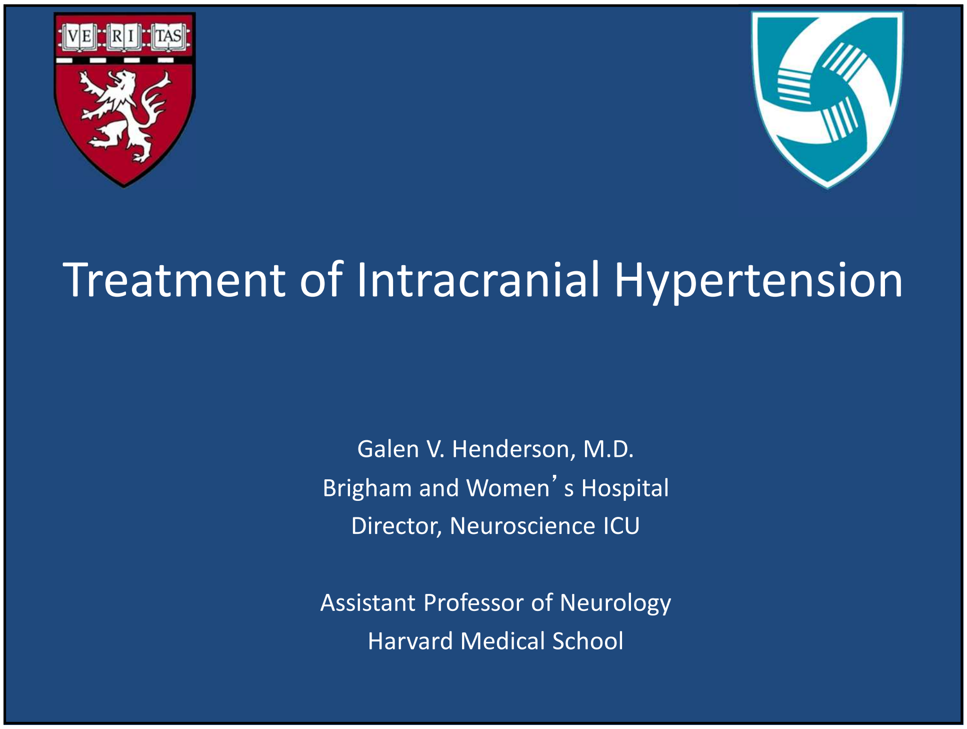


Answer to Question 5

- The answer is E.
- Echo to r/o PFO and to evaluate ejection fraction.
- EKG and Holter to r/o Afib.
- We always need brain imaging and neurovascular imaging

Thank you for your Attention

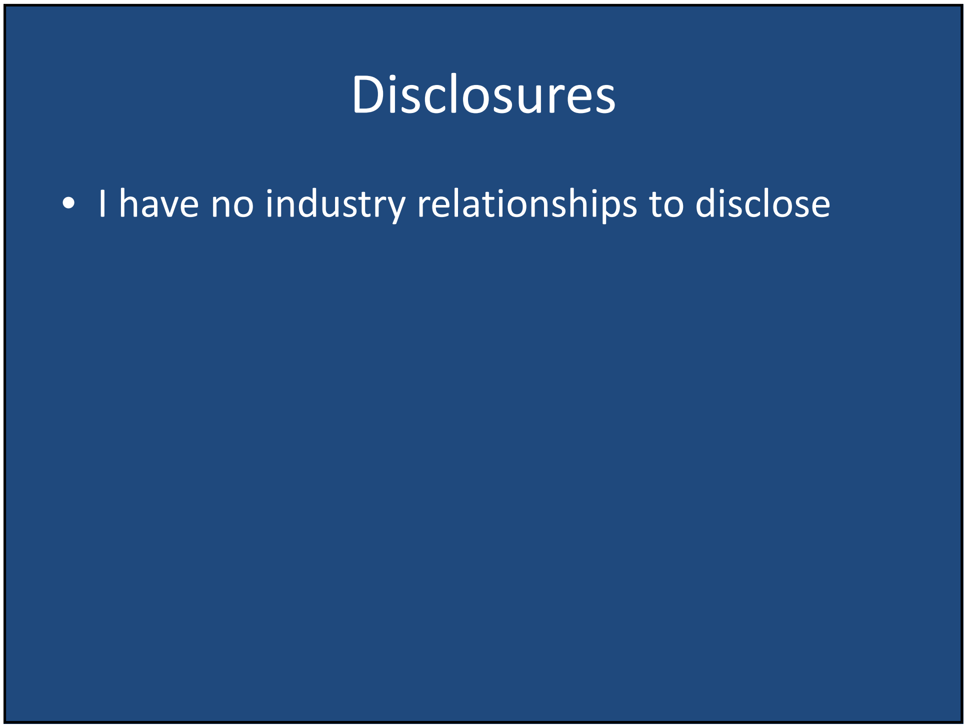




Treatment of Intracranial Hypertension

Galen V. Henderson, M.D.
Brigham and Women's Hospital
Director, Neuroscience ICU

Assistant Professor of Neurology
Harvard Medical School



Disclosures

- I have no industry relationships to disclose

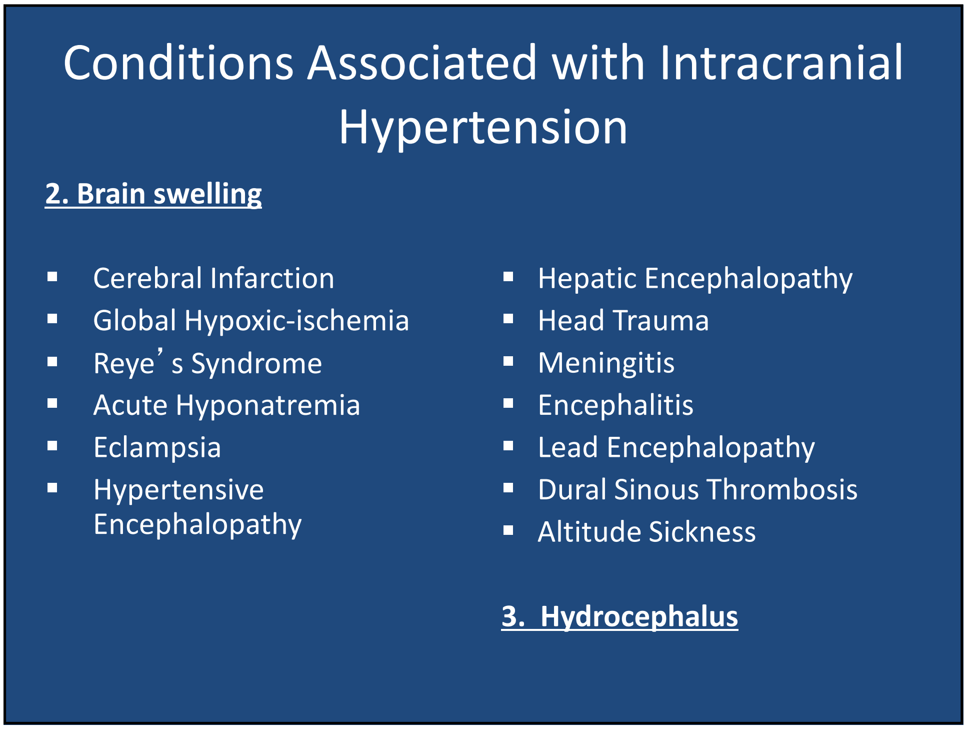
Outline

- Normal intracranial pressure
- Causes of intracranial HTN
- Herniation syndromes
- Medical management
- ICP monitoring
- Surgical management

Conditions Associated with Intracranial Hypertension

1. Mass lesions

- Cerebral Hemorrhage
  - Subdural
  - Epidural
  - Intracerebral
  - Subarachnoid
- Brain tumor
- Cerebral Abscess

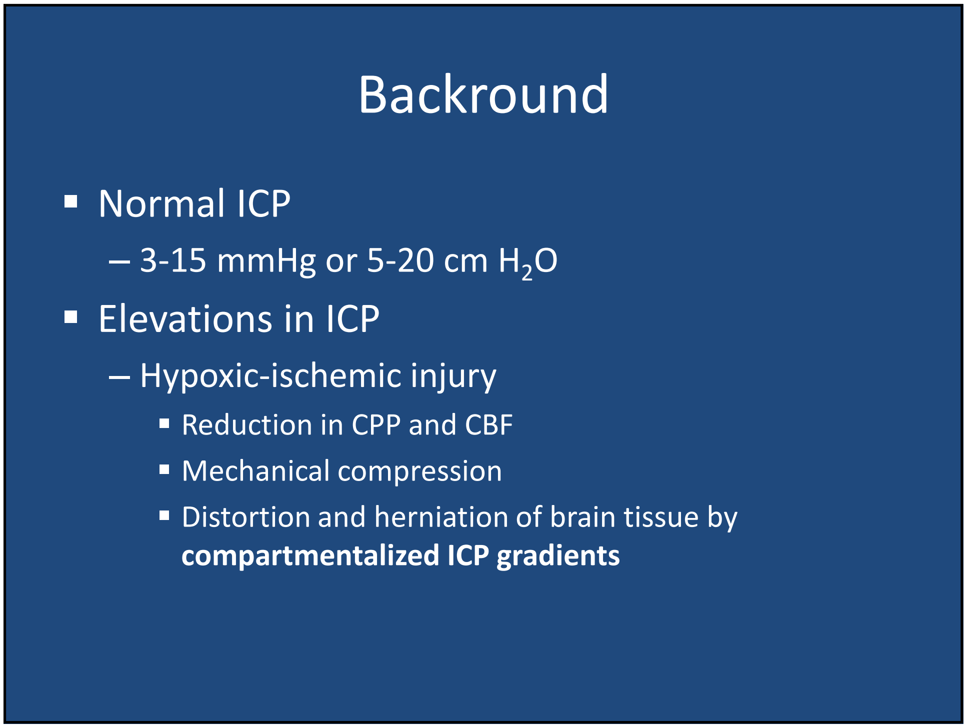


Conditions Associated with Intracranial Hypertension

2. Brain swelling

- Cerebral Infarction
- Global Hypoxic-ischemia
- Reye’s Syndrome
- Acute Hyponatremia
- Eclampsia
- Hypertensive Encephalopathy
- Hepatic Encephalopathy
- Head Trauma
- Meningitis
- Encephalitis
- Lead Encephalopathy
- Dural Sinous Thrombosis
- Altitude Sickness

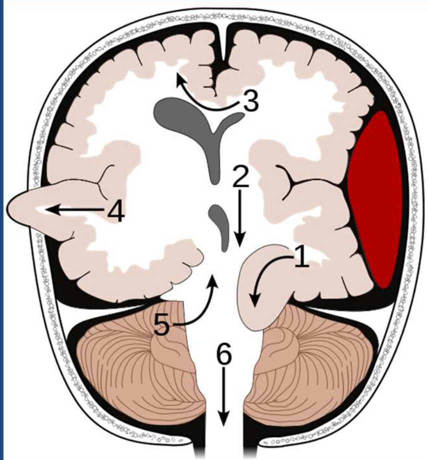
3. Hydrocephalus



Backround

- Normal ICP
  - 3-15 mmHg or 5-20 cm H_2O
- Elevations in ICP
  - Hypoxic-ischemic injury
    - Reduction in CPP and CBF
    - Mechanical compression
    - Distortion and herniation of brain tissue by **compartmentalized ICP gradients**

Cerebral Herniation Syndromes

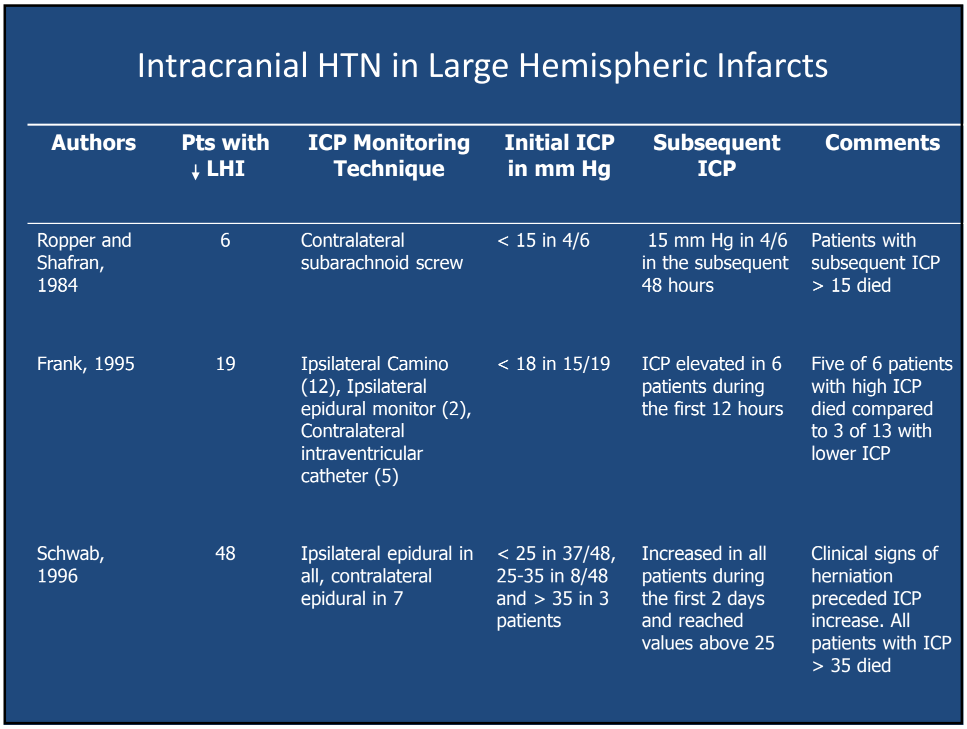


- Decreased cerebral perfusion pressure causing ischemia
- Midline shift causing ventricular obstruction
- Types
  1. Uncal
  2. Central (and # 6)
  3. Cingulate (subfalcine)
  4. Transcalvarial
  5. Cerebellar

Clinical Signs of Intracranial HTN

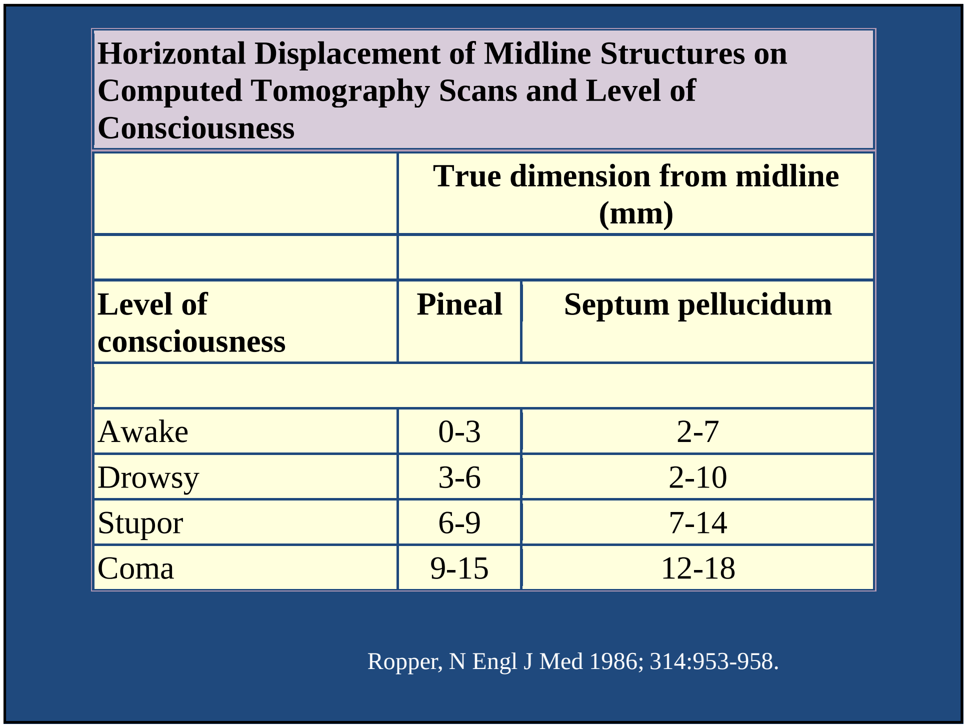
Combination of signs

- Depressed level of consciousness
- Reflex hypertension, with or without bradycardia
- Headache
- Vomiting
- Papilledema
- Cranial nerve palsies



Intracranial HTN in Large Hemispheric Infarcts

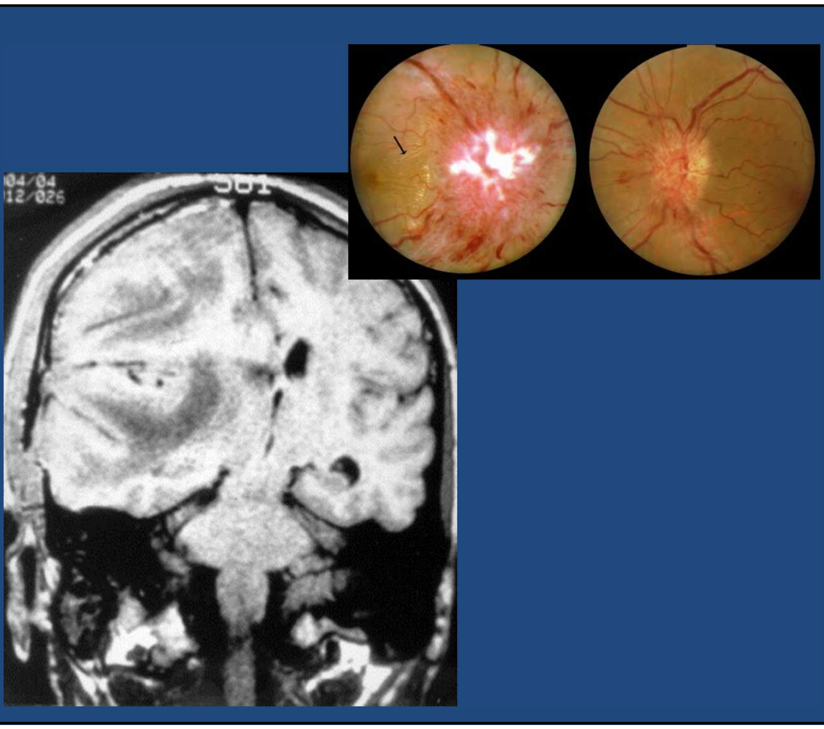
Authors	Pts with ↓ LHI	ICP Monitoring Technique	Initial ICP in mm Hg	Subsequent ICP	Comments
Ropper and Shafran, 1984	6	Contralateral subarachnoid screw	< 15 in 4/6	15 mm Hg in 4/6 in the subsequent 48 hours	Patients with subsequent ICP > 15 died
Frank, 1995	19	Ipsilateral Camino (12), Ipsilateral epidural monitor (2), Contralateral intraventricular catheter (5)	< 18 in 15/19	ICP elevated in 6 patients during the first 12 hours	Five of 6 patients with high ICP died compared to 3 of 13 with lower ICP
Schwab, 1996	48	Ipsilateral epidural in all, contralateral epidural in 7	< 25 in 37/48, 25-35 in 8/48 and > 35 in 3 patients	Increased in all patients during the first 2 days and reached values above 25	Clinical signs of herniation preceded ICP increase. All patients with ICP > 35 died



Horizontal Displacement of Midline Structures on Computed Tomography Scans and Level of Consciousness

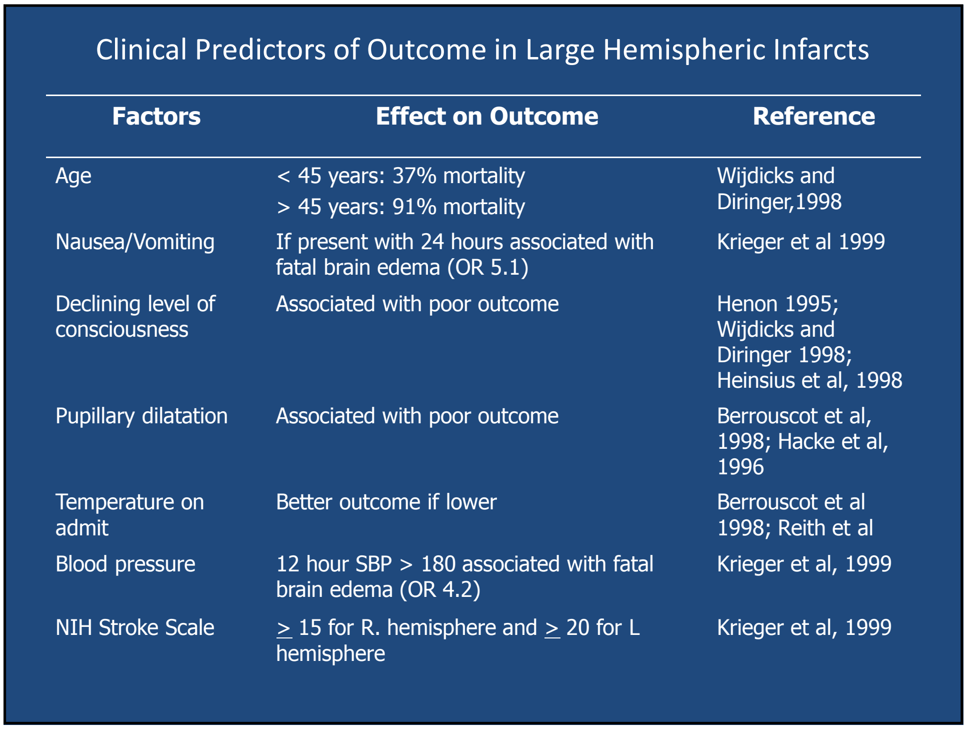
	True dimension from midline (mm)	
Level of consciousness	**Pineal**	**Septum pellucidum**
Awake	0-3	2-7
Drowsy	3-6	2-10
Stupor	6-9	7-14
Coma	9-15	12-18

Ropper, N Engl J Med 1986; 314:953-958.



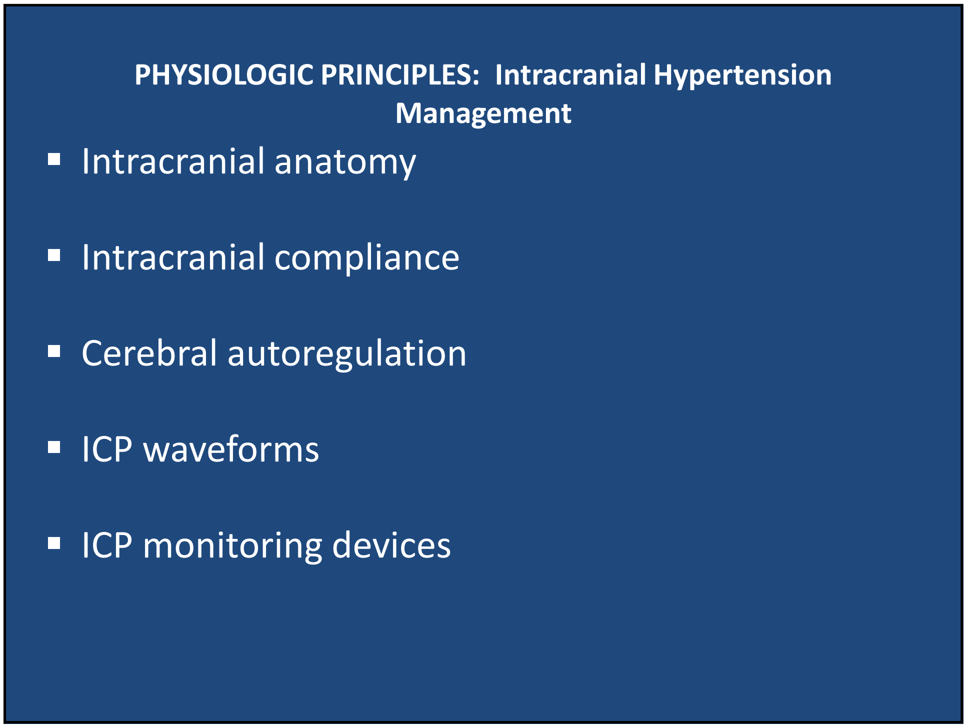
Outcomes of Large Hemispheric Infarcts

Author	Inclusion Criteria	Type of Study	No. of pts.	Morbidity and Mortality
Heinsius et al 1998	CT proven infarction 2/3 MCA territory	Hospital based registry	208	Mortality 17%, 50 major disability 1 mo
Heinsius et al 1998	CT infarction of entire MCA	Hospital based registry	72	Mortality 22%, major disability 64%
Frank, 1995	Depressed consciousness	NICU based	19	Mortality 42%
Wijdicks and Diringer, 1998	Infarct and edema < 24 hours	Retrospective	42	Mortality 55%
Ropper and Shafran, 1984	Stroke + drowsy + edema on CT	Prospective	12	Mortility 67%
Hacke et al, 1996		NICU based	55	Mortality 78%
Berrouschot et al, 1998		NICU based	53	Mortality 79%
Schwab et al 1996	Standard ICP protocol	NICU based	48	Mortality 81%



Clinical Predictors of Outcome in Large Hemispheric Infarcts

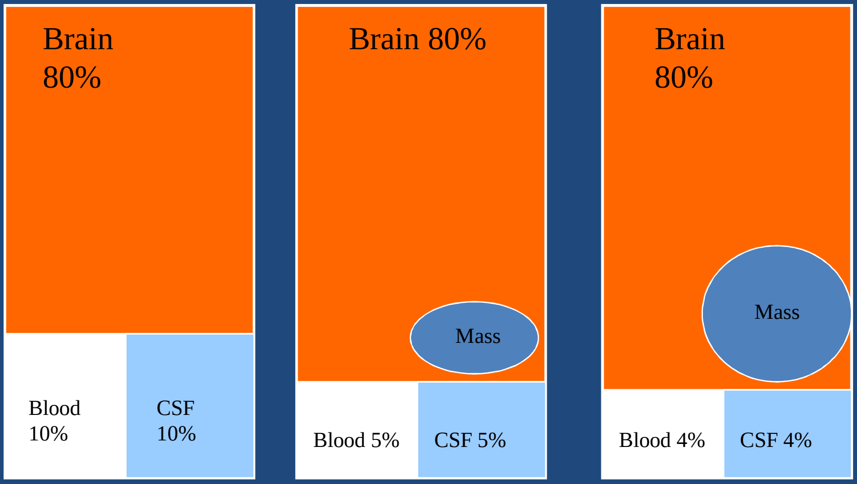
Factors	Effect on Outcome	Reference
Age	< 45 years: 37% mortality > 45 years: 91% mortality	Wijdicks and Diringer,1998
Nausea/Vomiting	If present with 24 hours associated with fatal brain edema (OR 5.1)	Krieger et al 1999
Declining level of consciousness	Associated with poor outcome	Henon 1995; Wijdicks and Diringer 1998; Heinsius et al, 1998
Pupillary dilatation	Associated with poor outcome	Berrouscot et al, 1998; Hacke et al, 1996
Temperature on admit	Better outcome if lower	Berrouscot et al 1998; Reith et al
Blood pressure	12 hour SBP > 180 associated with fatal brain edema (OR 4.2)	Krieger et al, 1999
NIH Stroke Scale	≥ 15 for R. hemisphere and ≥ 20 for L hemisphere	Krieger et al, 1999



PHYSIOLOGIC PRINCIPLES: Intracranial Hypertension Management

- Intracranial anatomy
- Intracranial compliance
- Cerebral autoregulation
- ICP waveforms
- ICP monitoring devices

Monroe Kellie Doctrine



Brain 80%

Blood 10%

CSF 10%

ICP 10mmHg

Brain 80%

Mass

Blood 5%

CSF 5%

ICP 15 mmHg

Brain 80%

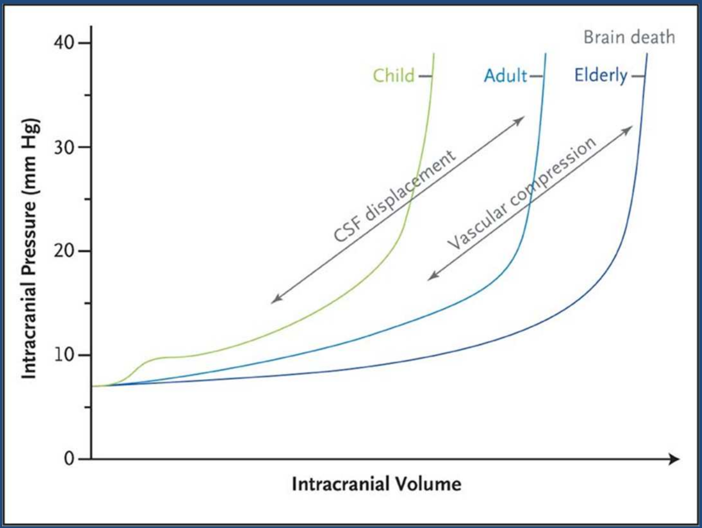
Mass

Blood 4%

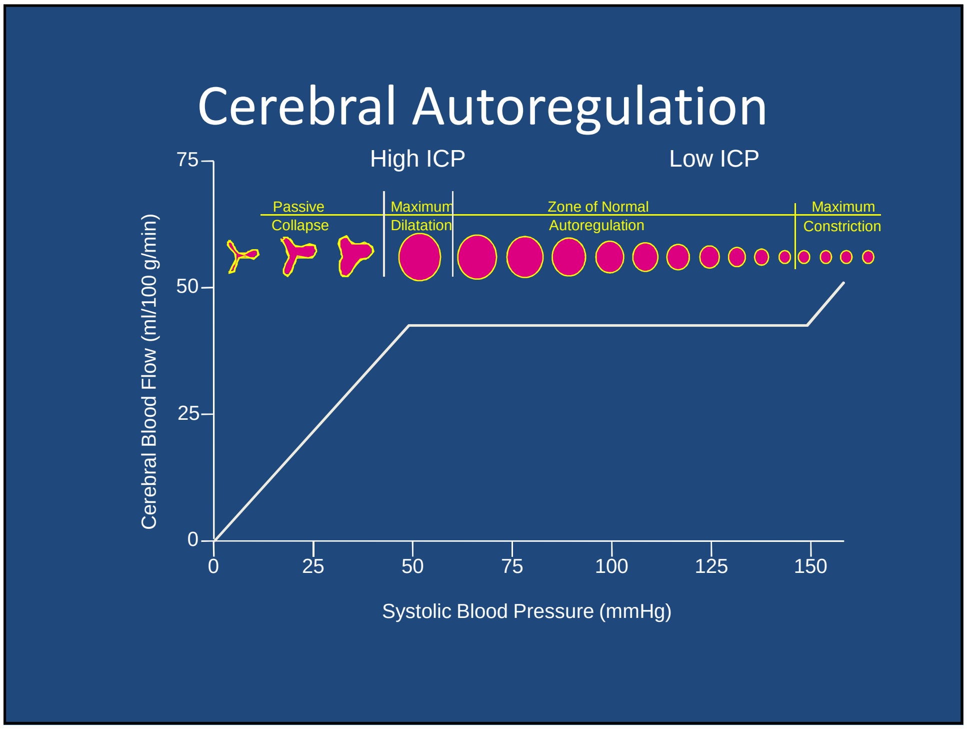
CSF 4%

ICP 30 mmHg

Relationship between Pressure and Volume within the Cranium.



Ropper AH. N Engl J Med 2012;367:746-752



Cerebral Autoregulation

Medical Management

General Measures

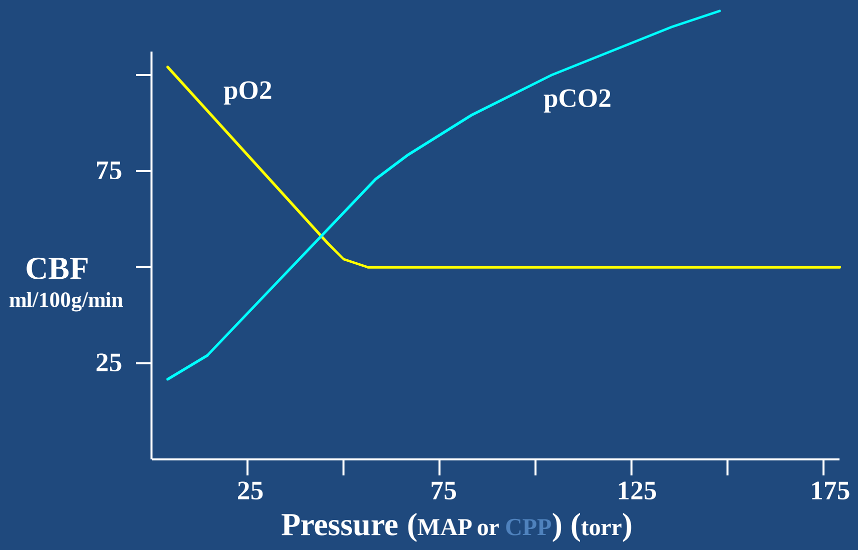
- Head position elevated 15-30^0 and in a neutral position avoid jugular compression
- Avoid hypotonic fluids
- Intubation only to protect airway
- Glucose management
- Osmolar therapy
- Agitation, fever, and seizures should be treated
- Blood pressure management
- Refractory Management
  - Hypothermia, barbituate therapy, decompressive hemicraniectomy

Initial Management

- Airway and Breathing
  - Loss of tone of the pharyngeal and glottic muscular causing airway obstruction
  - “Protect the airway”
  - Because intubation may be associated with a rise in ICP, consider
    - Lidocaine minimize coughing

Hyperventilation

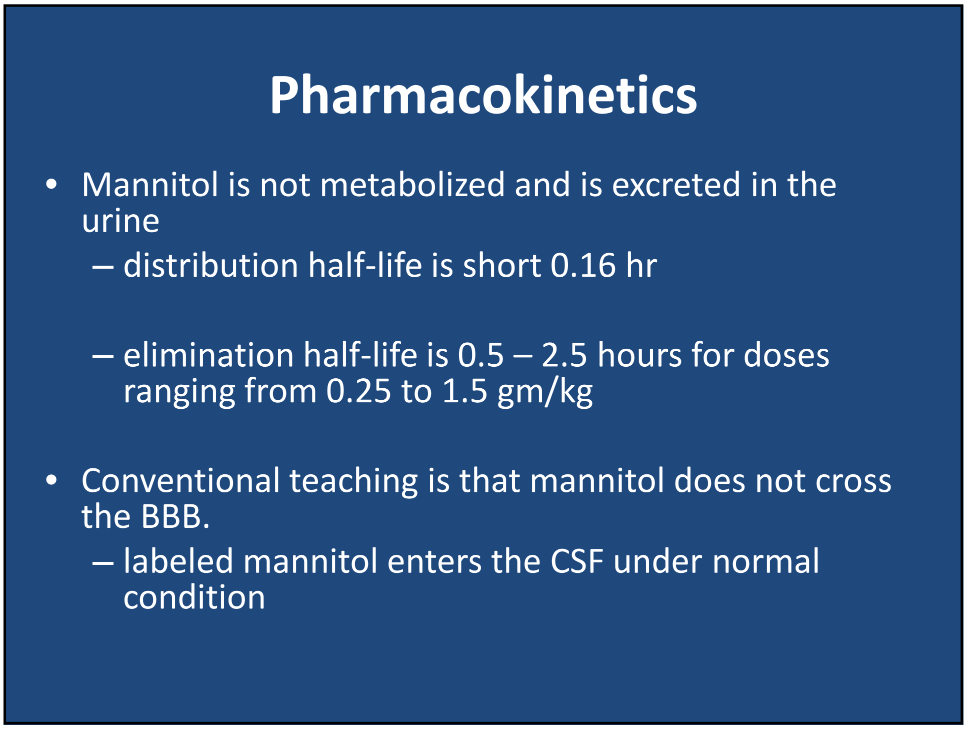
- Most effective treatment of acute herniation
- Vasoconstriction of cerebral blood vessels reducing flow
- Theoretical concern that it will induce/worsen ischemia
- Weaning prolonged hyperventilation, may lead to rebound increases in ICP
- Effects lasts 30 min. to hours
- Considered a temporizing measure only



Osmotherapy

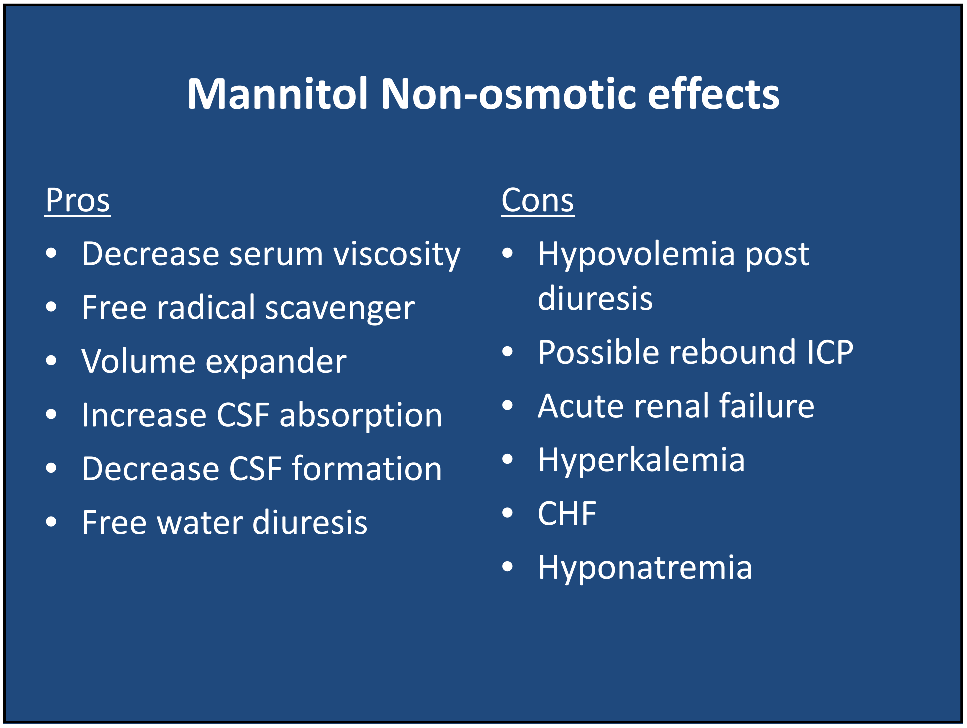
Classic teaching

- Mannitol acts by extracting water only from brain regions with intact blood-brain-barrier (BBB)
- Potential for mannitol accumulation and increase in cerebral edema in injured brain
  - could result in an increase in midline shift



Pharmacokinetics

- Mannitol is not metabolized and is excreted in the urine
  - distribution half-life is short 0.16 hr
  - elimination half-life is 0.5 – 2.5 hours for doses ranging from 0.25 to 1.5 gm/kg
- Conventional teaching is that mannitol does not cross the BBB.
  - labeled mannitol enters the CSF under normal condition



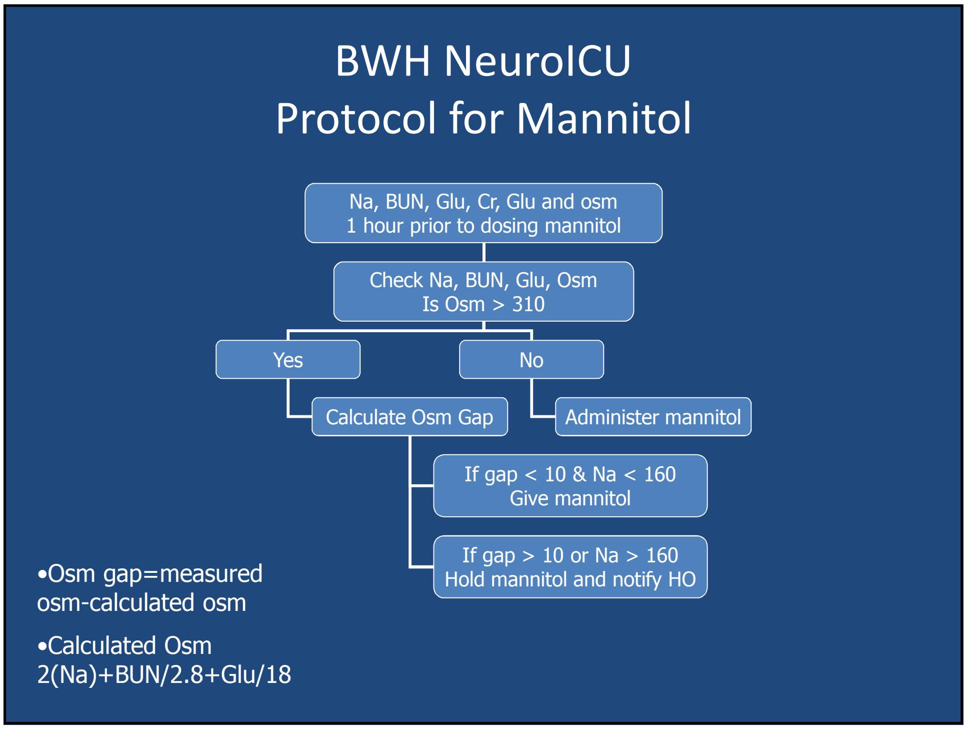
Mannitol Non-osmotic effects

Pros

- Decrease serum viscosity
- Free radical scavenger
- Volume expander
- Increase CSF absorption
- Decrease CSF formation
- Free water diuresis

Cons

- Hypovolemia post diuresis
- Possible rebound ICP
- Acute renal failure
- Hyperkalemia
- CHF
- Hyponatremia



BWH NeuroICU
Protocol for Mannitol

Na, BUN, Glu, Cr, Glu and osm
1 hour prior to dosing mannitol

Check Na, BUN, Glu, Osm
Is Osm > 310

Yes

Calculate Osm Gap

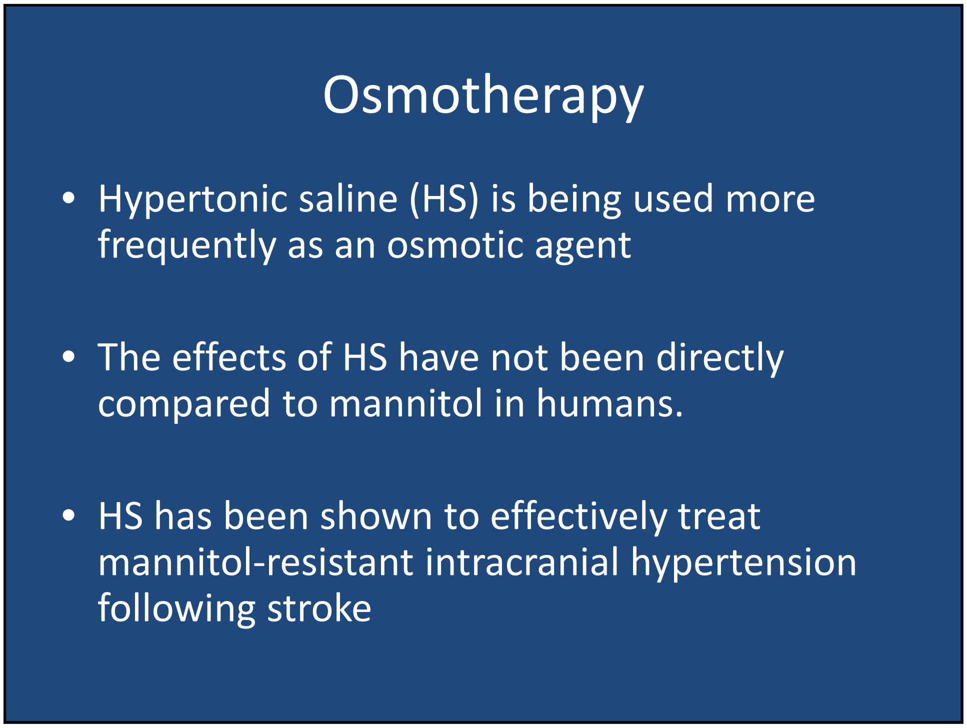
If gap < 10 & Na < 160
Give mannitol

If gap > 10 or Na > 160
Hold mannitol and notify HO

No

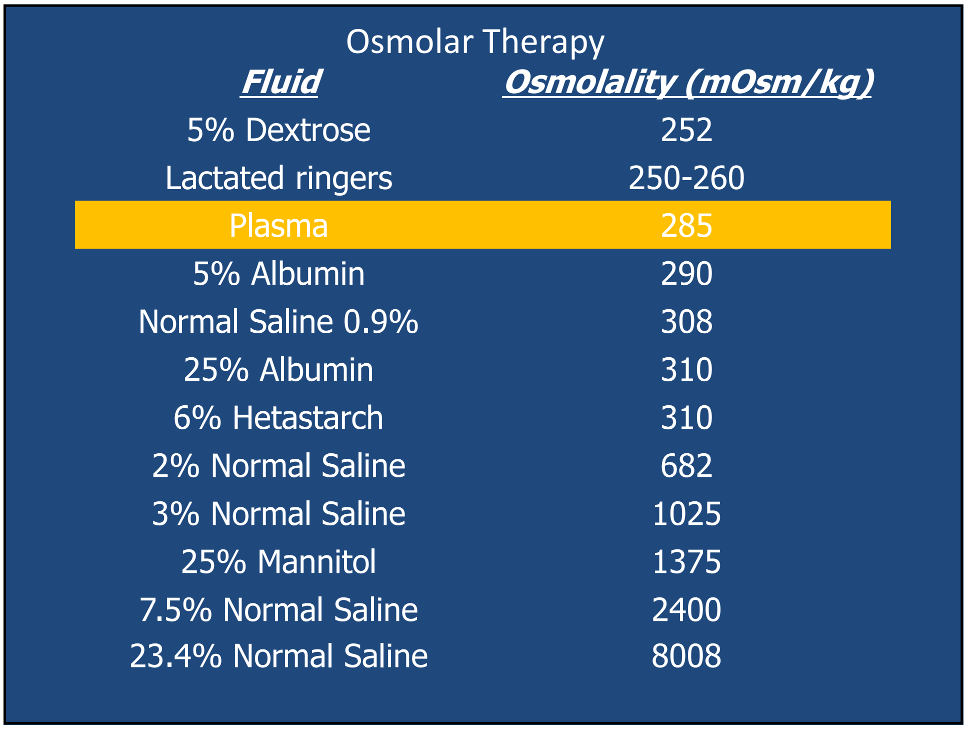
Administer mannitol

- Osm gap=measured osm-calculated osm
- Calculated Osm 2(Na)+BUN/2.8+Glu/18



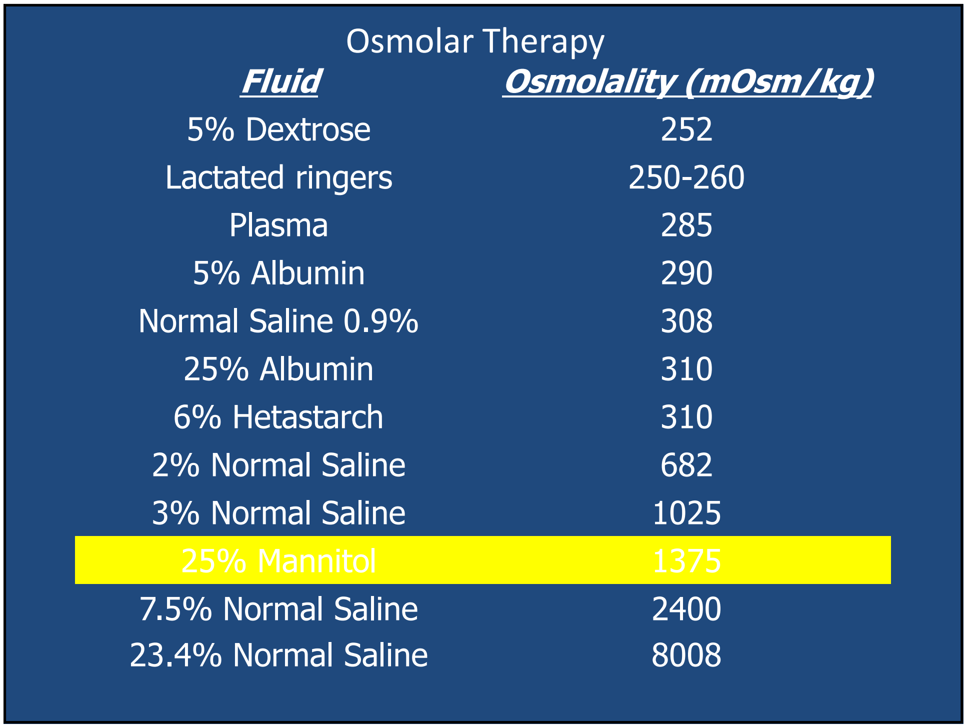
Osmotherapy

- Hypertonic saline (HS) is being used more frequently as an osmotic agent
- The effects of HS have not been directly compared to mannitol in humans.
- HS has been shown to effectively treat mannitol-resistant intracranial hypertension following stroke



Osmolar Therapy

Fluid	***Osmolality (mOsm/kg)***
5% Dextrose	252
Lactated ringers	250-260
Plasma	285
5% Albumin	290
Normal Saline 0.9%	308
25% Albumin	310
6% Hetastarch	310
2% Normal Saline	682
3% Normal Saline	1025
25% Mannitol	1375
7.5% Normal Saline	2400
23.4% Normal Saline	8008



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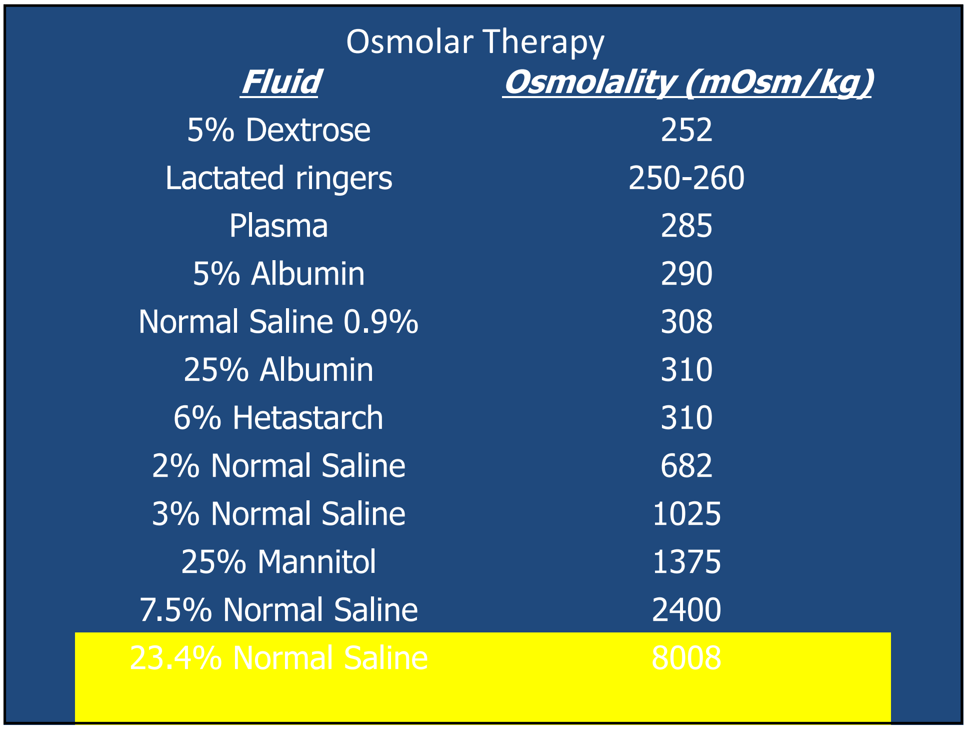

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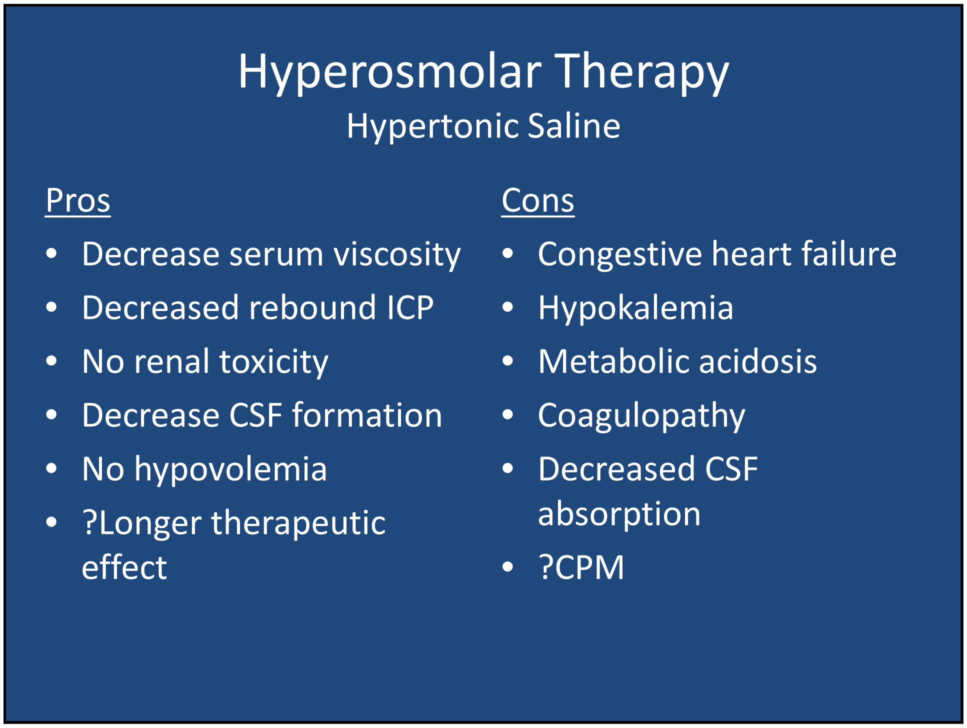


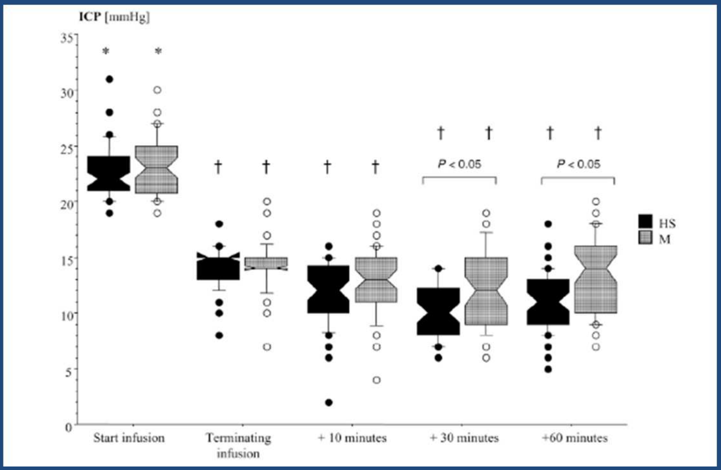
Hyperosmolar Therapy

Hypertonic Saline

Pros	Cons
• Decrease serum viscosity	• Congestive heart failure
• Decreased rebound ICP	• Hypokalemia
• No renal toxicity	• Metabolic acidosis
• Decrease CSF formation	• Coagulopathy
• No hypovolemia	• Decreased CSF absorption
• ?Longer therapeutic effect	• ?CPM

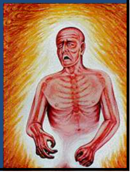
7.2% Hypertonic Saline vs 15% Mannitol Solution for Treating ICP in Neurosurgical Patients

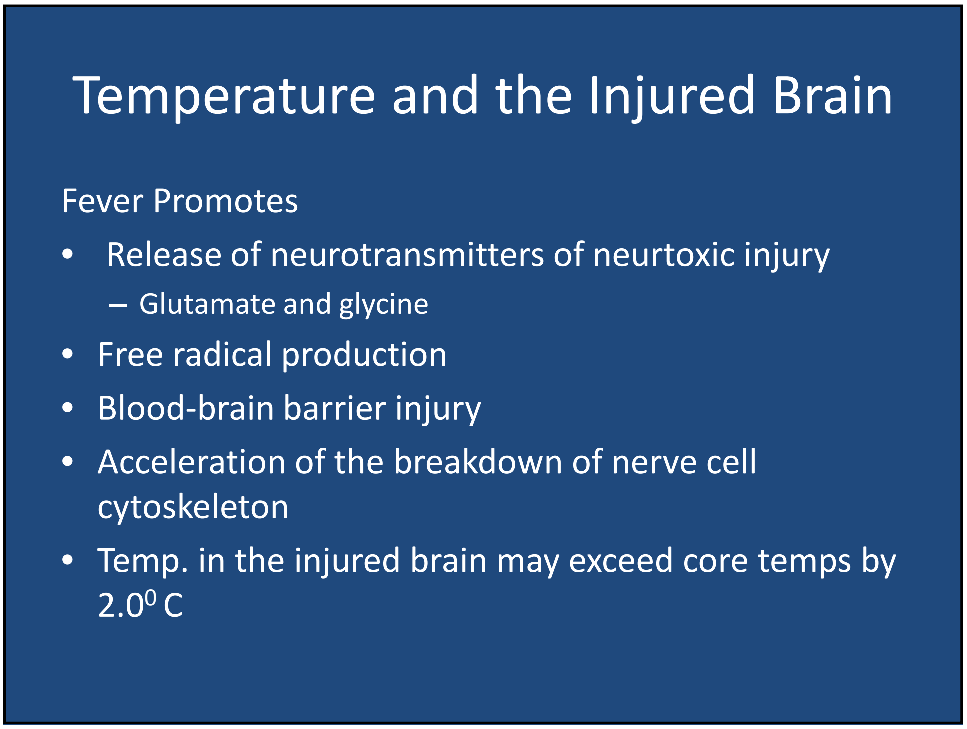
Critical Care 2005;9:R530



Temperature and the Injured Brain

- Fever worsens outcome:
  - for every 1° C rise in temp, risk of poor outcome doubles (Reith, Lancet 1996)
- Treat aggressively with acetaminophen, ibuprofen, or both
- Fever should be treated with antipyretics or device
- Lowering the elevated body temperature may improve prognosis
- Hypothermia has been shown to be neuroprotective

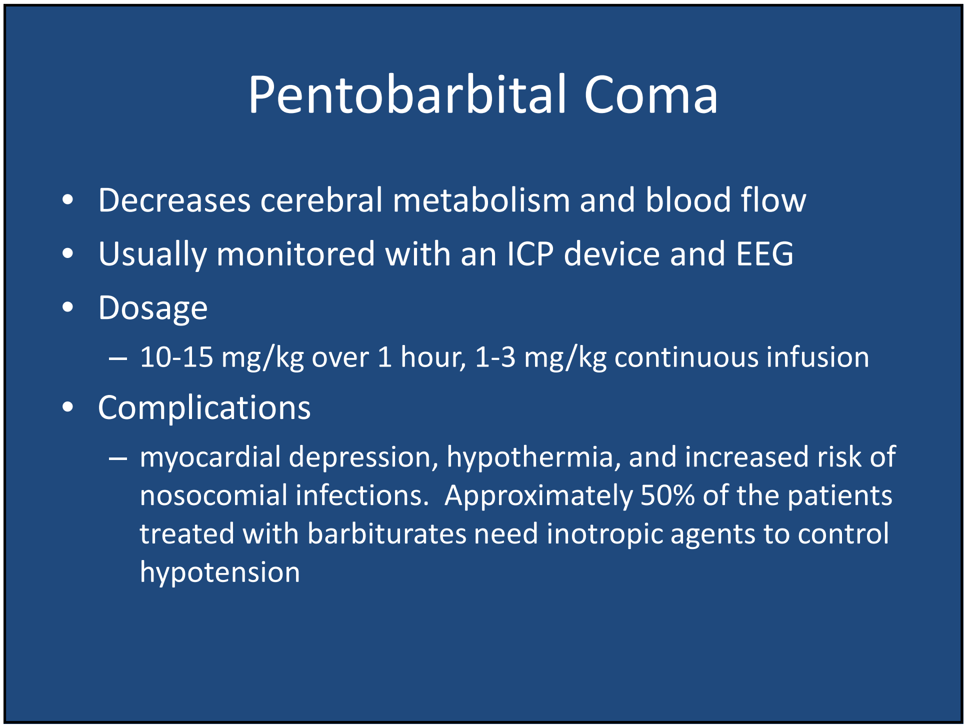




Temperature and the Injured Brain

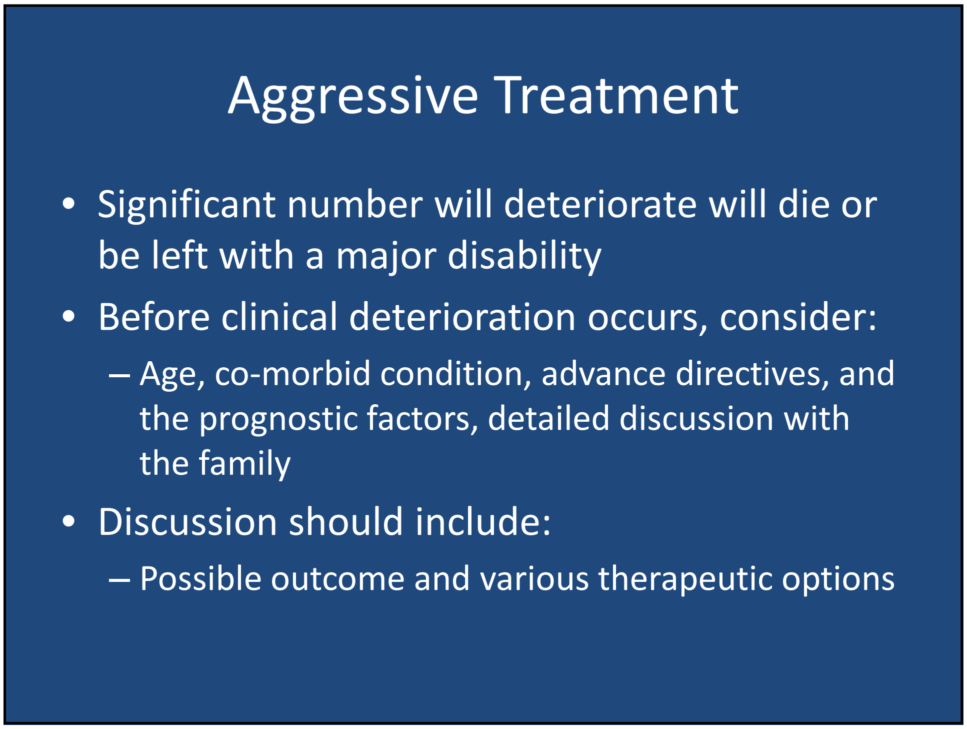
Fever Promotes

- Release of neurotransmitters of neurtoxic injury
  - Glutamate and glycine
- Free radical production
- Blood-brain barrier injury
- Acceleration of the breakdown of nerve cell cytoskeleton
- Temp. in the injured brain may exceed core temps by 2.0^0 C



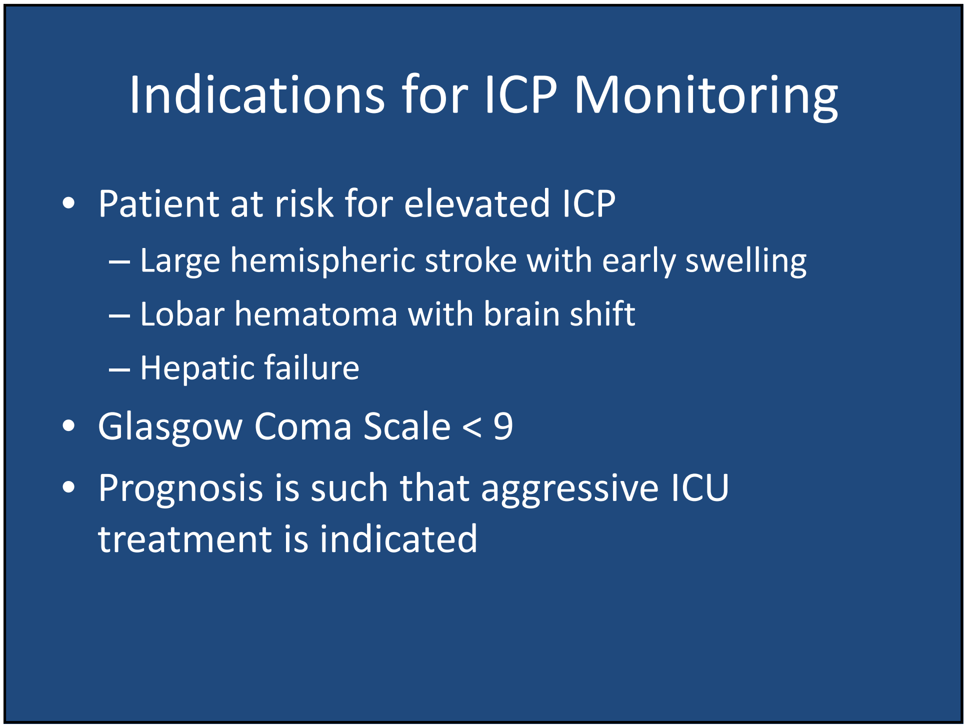
Pentobarbital Coma

- Decreases cerebral metabolism and blood flow
- Usually monitored with an ICP device and EEG
- Dosage
  - 10-15 mg/kg over 1 hour, 1-3 mg/kg continuous infusion
- Complications
  - myocardial depression, hypothermia, and increased risk of nosocomial infections. Approximately 50% of the patients treated with barbiturates need inotropic agents to control hypotension



Aggressive Treatment

- Significant number will deteriorate will die or be left with a major disability
- Before clinical deterioration occurs, consider:
  - Age, co-morbid condition, advance directives, and the prognostic factors, detailed discussion with the family
- Discussion should include:
  - Possible outcome and various therapeutic options

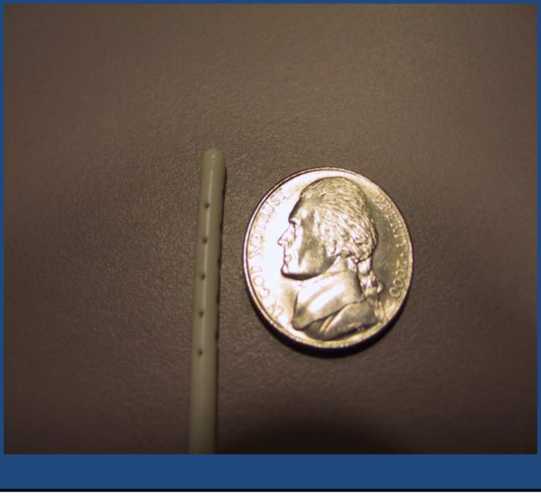


Indications for ICP Monitoring

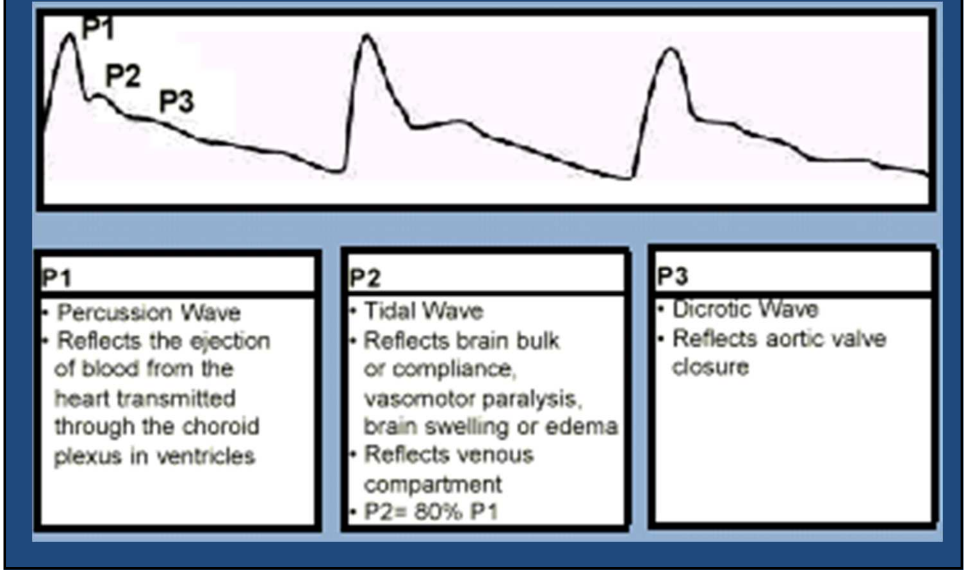
- Patient at risk for elevated ICP
  - Large hemispheric stroke with early swelling
  - Lobar hematoma with brain shift
  - Hepatic failure
- Glasgow Coma Scale < 9
- Prognosis is such that aggressive ICU treatment is indicated

Intracranial Pressure Monitors

	Advantages	*Disadvantages*
Ventricular catheter	Accurate, reliable, drains CSF	Highest infection rate, ext. tranducer
Parenchymal monitors	Easily placed, low infection rate	Cannot drain CSF, cannot be rezeroed
Epidural bolts	No brain penetration	Not reliable
Subarachnoid bolts	No brain penetration	Not reliable



Intracranial Pressure Waves



P1

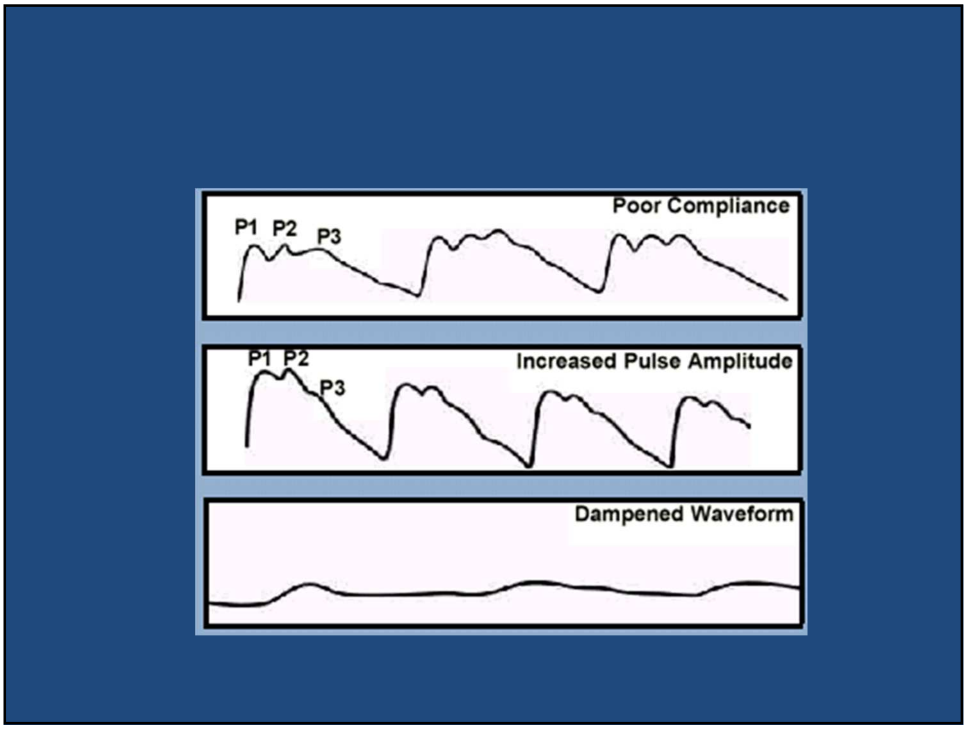
- Percussion Wave
- Reflects the ejection of blood from the heart transmitted through the choroid plexus in ventricles

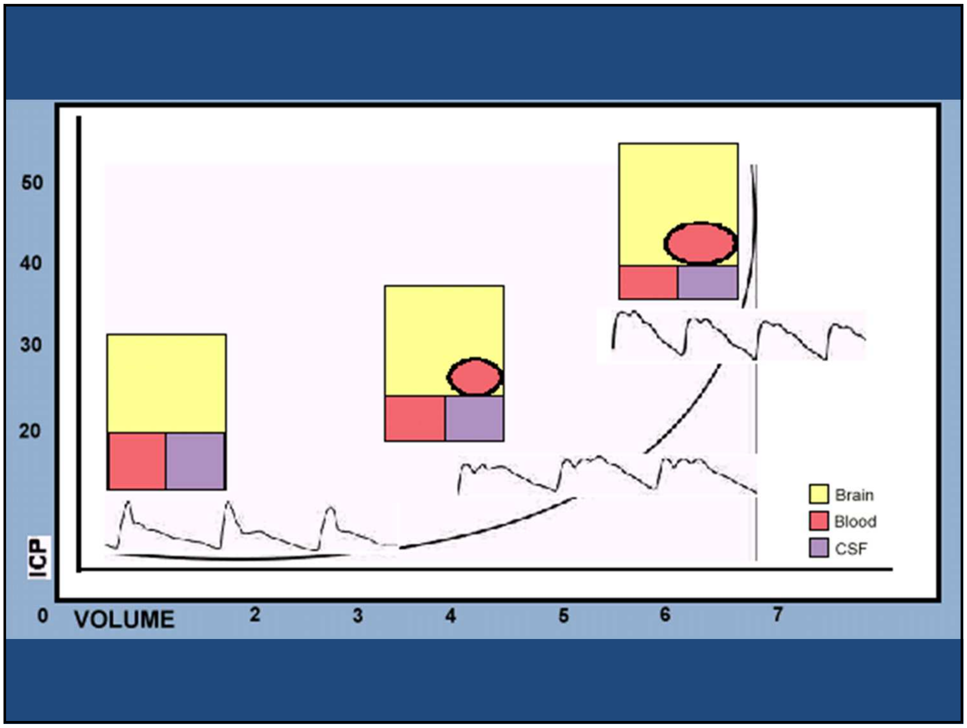
P2

- Tidal Wave
- Reflects brain bulk or compliance, vasomotor paralysis, brain swelling or edema
- Reflects venous compartment
- P2= 80% P1

P3

- Dicrotic Wave
- Reflects aortic valve closure


Poor Compliance
P1
P2
P3
Increased Pulse Amplitude
P1
P2
P3
Dampened Waveform


50
40
30
20
ICP
0
VOLUME
2
3
4
5
6
7
Brain
Blood
CSF

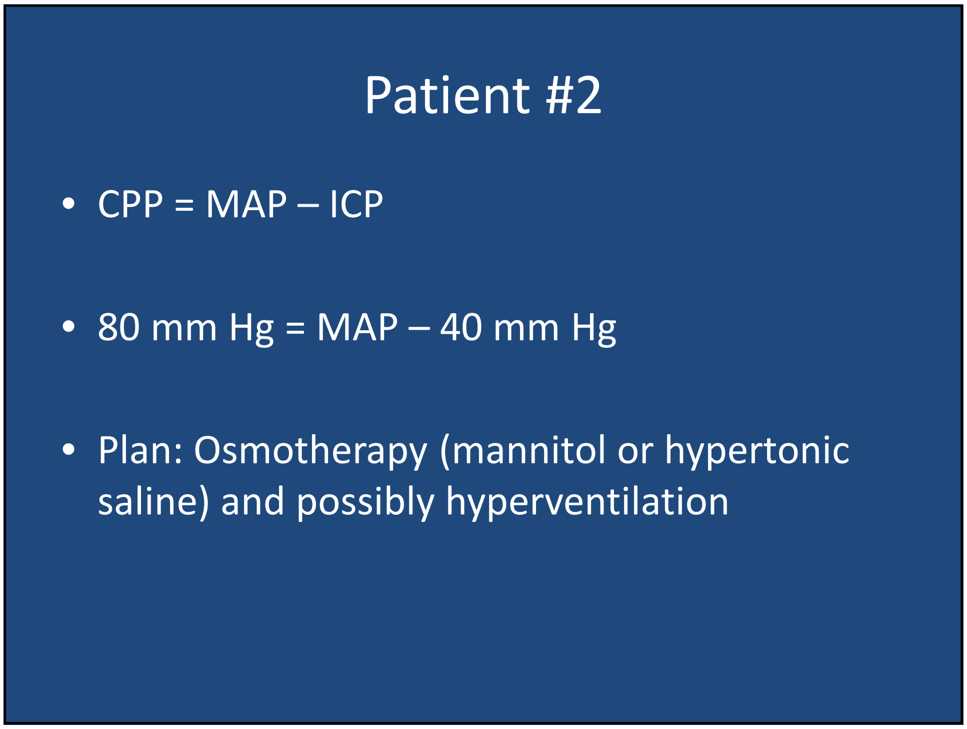
Patient #1

- CPP = MAP – ICP
- 40mm Hg = MAP – 40 mm Hg
- Plan: CPP optimization and consider a vasopressor

Pressor Reference Guide

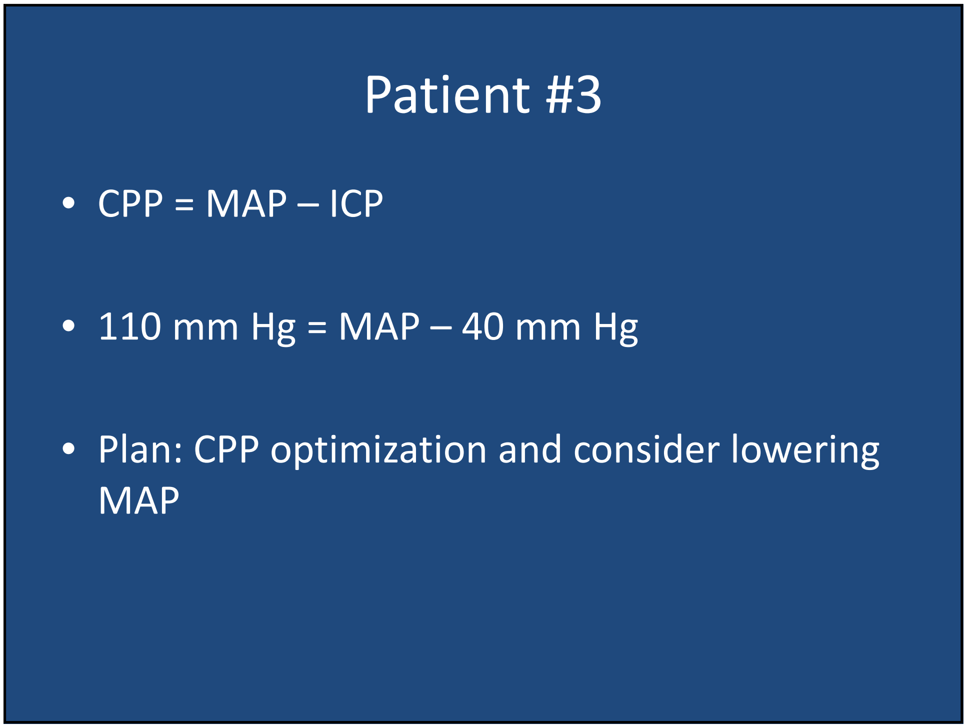
		HR	**MABP**	**RBF**
Dopamine*	1- 4	-	-	↑
	5-20	↑	↑	↑↑
Dobutamine*	2-10	↑	↑	↑
Norepinephrine⁺ (levophed)	2-20	↑	↑↑↑	↑
Phenylephrine⁺ (Neo-Synephrine)	2-200	↓	↑↑	↓

* µg/kg/min ⁺ µg/min



Patient #2

- CPP = MAP – ICP
- 80 mm Hg = MAP – 40 mm Hg
- Plan: Osmotherapy (mannitol or hypertonic saline) and possibly hyperventilation



Patient #3

- CPP = MAP – ICP
- 110 mm Hg = MAP – 40 mm Hg
- Plan: CPP optimization and consider lowering MAP

Antihypertensives

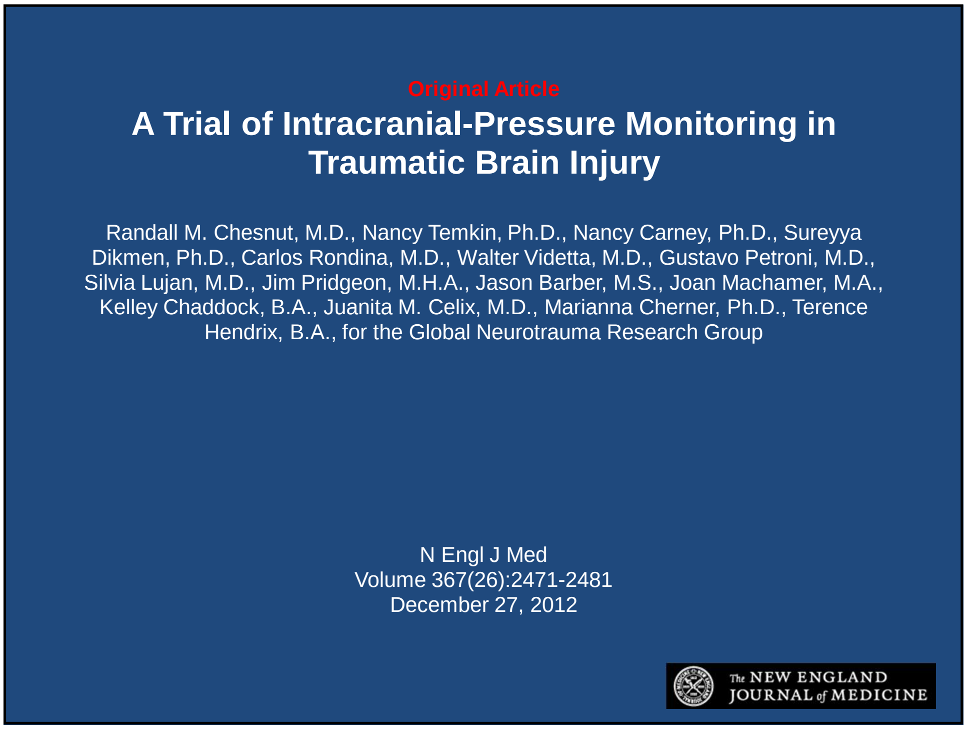
- Nitrates
  - Nitroprusside – cyanide poison, excessive hypotension
  - Nitroglycerin – excessive hypotension
- Beta blockers – blunts the sympathetic response
  - Esmolol
  - Labetalol
- ACE-I – no control, long acting
  - Enalaprat
- Calcium channel blockers - cost
  - Nicardipine (best safety profile, no surprises, zero order kinetics)

Sedative Drugs

Generic Name:	**Midazolam**	**Diazepam**	**Lorazepam**	**Propofol**
Trade Name:	**Versed®**	**Valium®**	**Ativan®**	**Diprivan®**
Loading dose[a] µg/kg	1-5 mg	1-10 mg	1-5 mg	0.25-0.75
Infusion rate[a] µg/kg/min	1-20 mg/hr	NR	0.5-5 mg/hr	10-100
Onset of action	**Fast**	**Slow**	**Slow**	**Rapid**
Active metabolites	**Yes**	**Yes**	**No**	**No**
Prolonged awakening	**Yes**	**Yes**	**Yes**	**Infrequent**
Direct cost ($)	**High**	**Low**	**Low**	**High**

a Titrated to effect

NR, not recommended



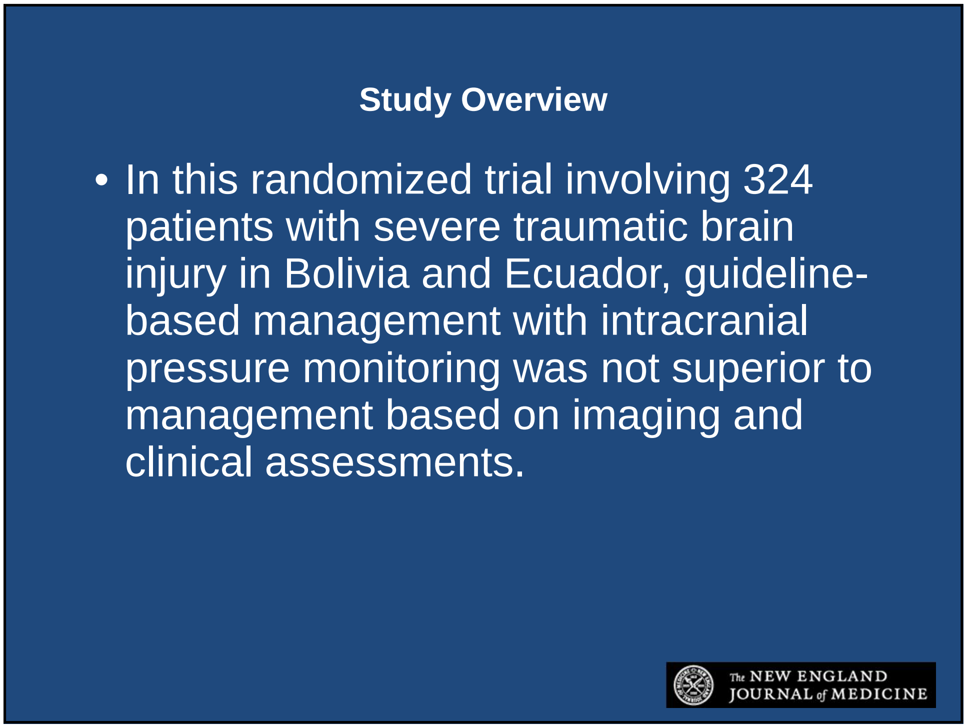
Original Article

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

Randall M. Chesnut, M.D., Nancy Temkin, Ph.D., Nancy Carney, Ph.D., Sureyya Dikmen, Ph.D., Carlos Rondina, M.D., Walter Videtta, M.D., Gustavo Petroni, M.D., Silvia Lujan, M.D., Jim Pridgeon, M.H.A., Jason Barber, M.S., Joan Machamer, M.A., Kelley Chaddock, B.A., Juanita M. Celix, M.D., Marianna Cherner, Ph.D., Terence Hendrix, B.A., for the Global Neurotrauma Research Group

N Engl J Med
Volume 367(26):2471-2481
December 27, 2012

The NEW ENGLAND JOURNAL of MEDICINE



Study Overview

- In this randomized trial involving 324 patients with severe traumatic brain injury in Bolivia and Ecuador, guideline-based management with intracranial pressure monitoring was not superior to management based on imaging and clinical assessments.

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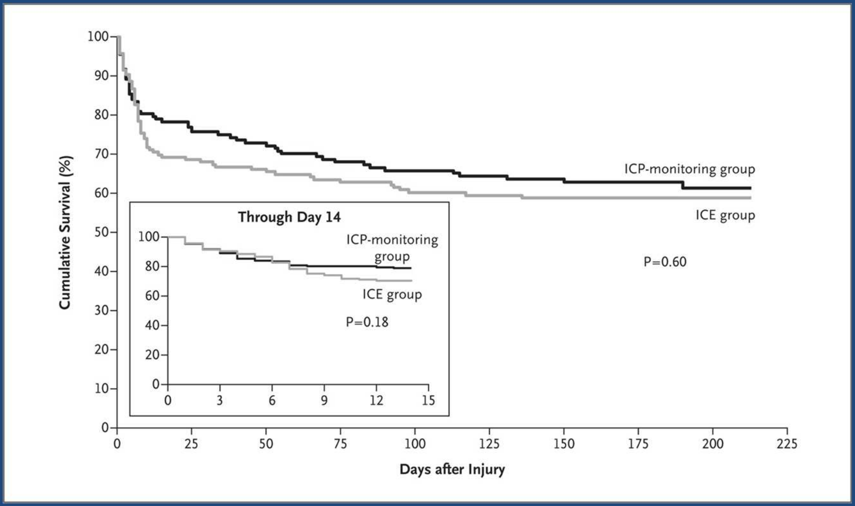
Cumulative Survival Rate According to Study Group.



Chesnut RM et al. N Engl J Med 2012;367:2471-2481

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Clinical Outcomes.

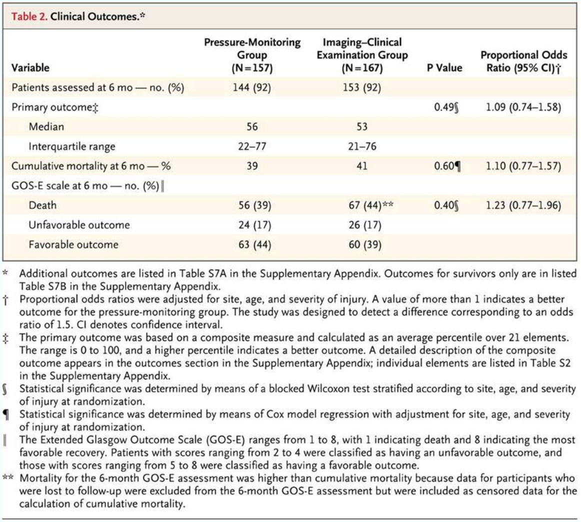

Table 2. Clinical Outcomes.*

Variable	Pressure-Monitoring Group (N=157)	Imaging–Clinical Examination Group (N=167)	P Value	Proportional Odds Ratio (95% CI)†
Patients assessed at 6 mo — no. (%)	144 (92)	153 (92)		
Primary outcome‡			0.49§	1.09 (0.74–1.58)
Median	56	53		
Interquartile range	22–77	21–76		
Cumulative mortality at 6 mo — %	39	41	0.60¶	1.10 (0.77–1.57)
GOS-E scale at 6 mo — no. (%)‖				
Death	56 (39)	67 (44)**	0.40§	1.23 (0.77–1.96)
Unfavorable outcome	24 (17)	26 (17)		
Favorable outcome	63 (44)	60 (39)		

* Additional outcomes are listed in Table S7A in the Supplementary Appendix. Outcomes for survivors only are in listed Table S7B in the Supplementary Appendix.

† Proportional odds ratios were adjusted for site, age, and severity of injury. A value of more than 1 indicates a better outcome for the pressure-monitoring group. The study was designed to detect a difference corresponding to an odds ratio of 1.5. CI denotes confidence interval.

‡ The primary outcome was based on a composite measure and calculated as an average percentile over 21 elements. The range is 0 to 100, and a higher percentile indicates a better outcome. A detailed description of the composite outcome appears in the outcomes section in the Supplementary Appendix; individual elements are listed in Table S2 in the Supplementary Appendix.

§ Statistical significance was determined by means of a blocked Wilcoxon test stratified according to site, age, and severity of injury at randomization.

¶ Statistical significance was determined by means of Cox model regression with adjustment for site, age, and severity of injury at randomization.

‖ The Extended Glasgow Outcome Scale (GOS-E) ranges from 1 to 8, with 1 indicating death and 8 indicating the most favorable recovery. Patients with scores ranging from 2 to 4 were classified as having an unfavorable outcome, and those with scores ranging from 5 to 8 were classified as having a favorable outcome.

** Mortality for the 6-month GOS-E assessment was higher than cumulative mortality because data for participants who were lost to follow-up were excluded from the 6-month GOS-E assessment but were included as censored data for the calculation of cumulative mortality.

Chesnut RM et al. N Engl J Med 2012;367:2471-2481

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Catheter-Related or Serious Adverse Events.

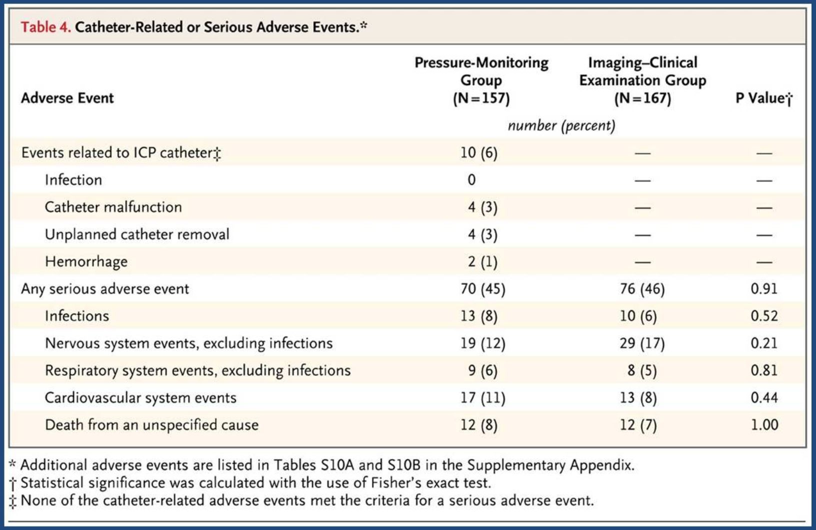


Table 4. Catheter-Related or Serious Adverse Events.*

Adverse Event	Pressure-Monitoring Group (N=157)	Imaging–Clinical Examination Group (N=167)	P Value†
	number (percent)		
Events related to ICP catheter‡	10 (6)	—	—
Infection	0	—	—
Catheter malfunction	4 (3)	—	—
Unplanned catheter removal	4 (3)	—	—
Hemorrhage	2 (1)	—	—
Any serious adverse event	70 (45)	76 (46)	0.91
Infections	13 (8)	10 (6)	0.52
Nervous system events, excluding infections	19 (12)	29 (17)	0.21
Respiratory system events, excluding infections	9 (6)	8 (5)	0.81
Cardiovascular system events	17 (11)	13 (8)	0.44
Death from an unspecified cause	12 (8)	12 (7)	1.00

* Additional adverse events are listed in Tables S10A and S10B in the Supplementary Appendix.

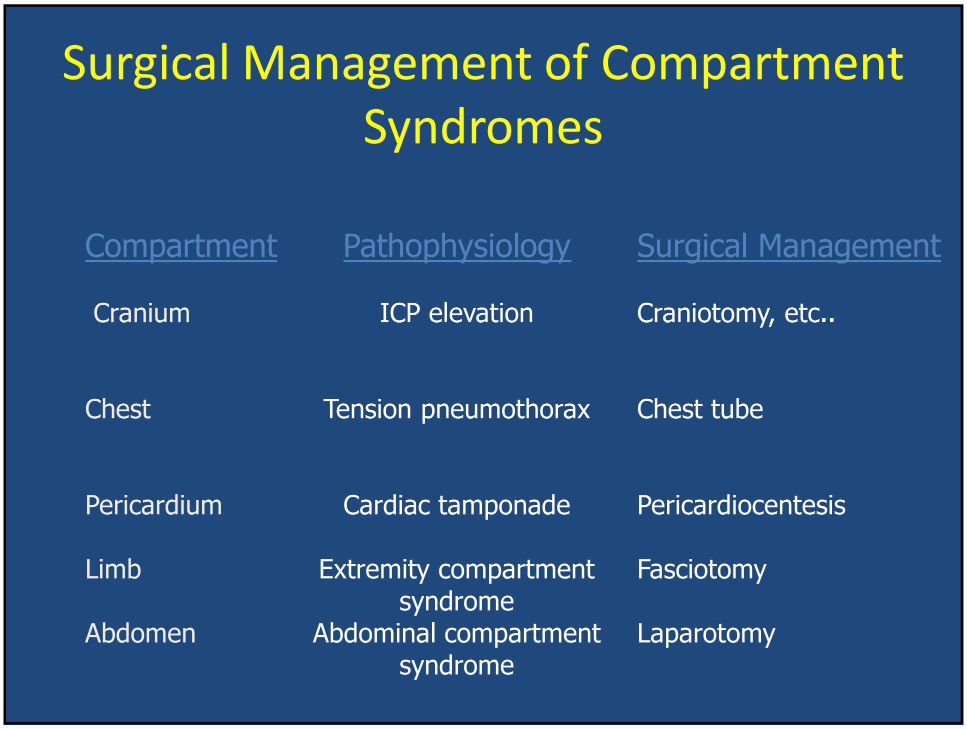
† Statistical significance was calculated with the use of Fisher's exact test.

‡ None of the catheter-related adverse events met the criteria for a serious adverse event.

Chesnut RM et al. N Engl J Med 2012;367:2471-2481

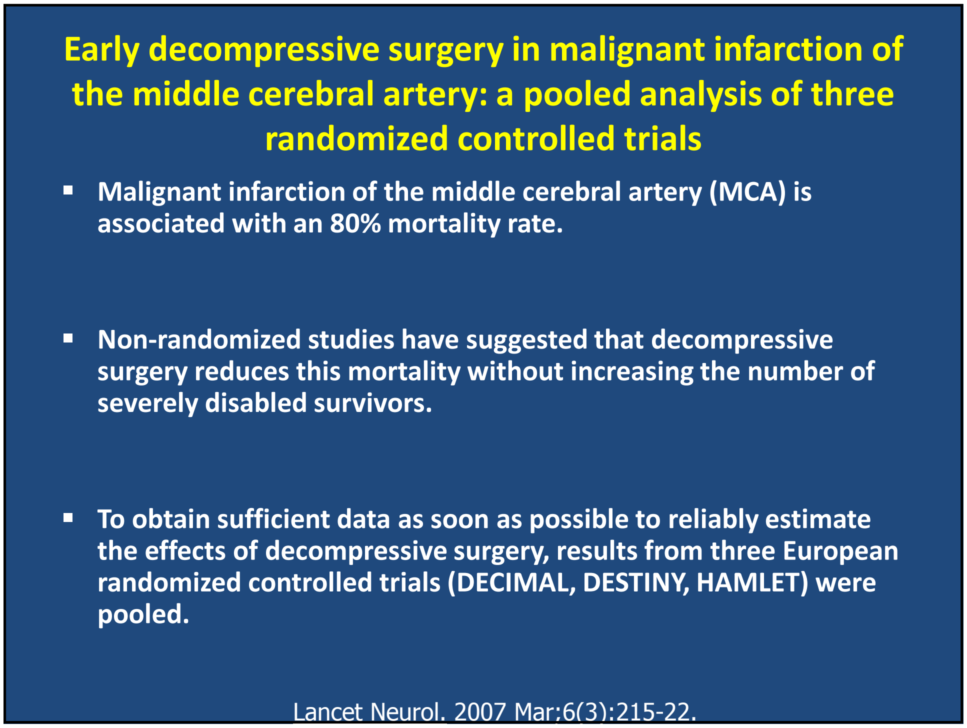
Conclusions

- For patients with severe traumatic brain injury, care focused on maintaining monitored intracranial pressure at 20 mm Hg or less was not shown to be superior to care based on imaging and clinical examination.



Surgical Management of Compartment Syndromes

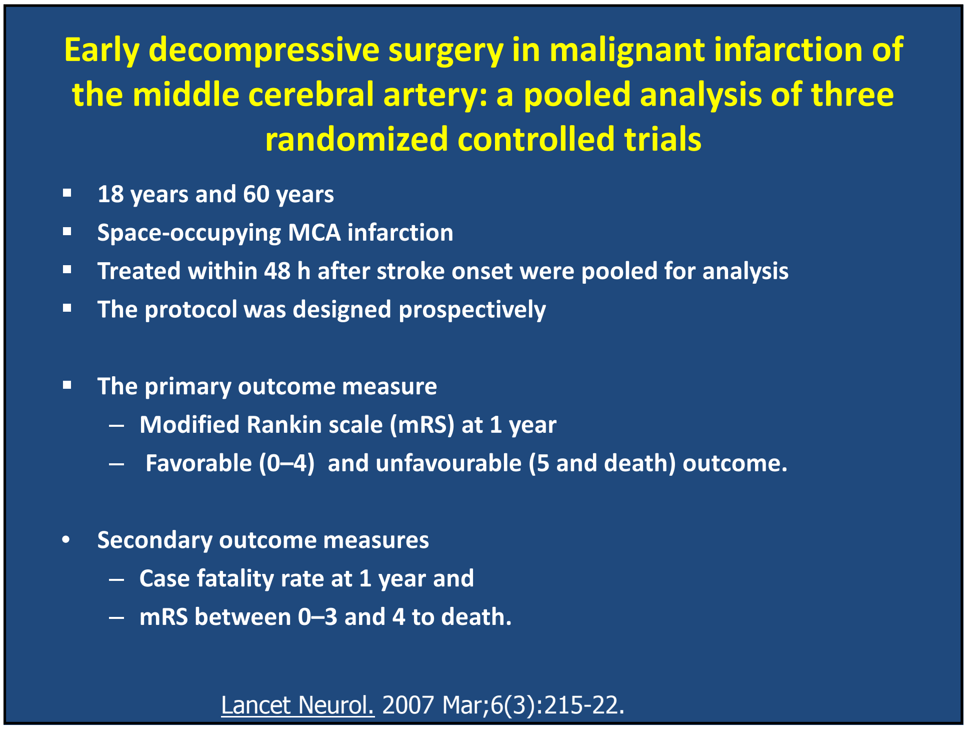
Compartment	Pathophysiology	Surgical Management
Cranium	ICP elevation	Craniotomy, etc..
Chest	Tension pneumothorax	Chest tube
Pericardium	Cardiac tamponade	Pericardiocentesis
Limb	Extremity compartment syndrome	Fasciotomy
Abdomen	Abdominal compartment syndrome	Laparotomy



Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomized controlled trials

- **Malignant infarction of the middle cerebral artery (MCA) is associated with an 80% mortality rate.**
- **Non-randomized studies have suggested that decompressive surgery reduces this mortality without increasing the number of severely disabled survivors.**
- **To obtain sufficient data as soon as possible to reliably estimate the effects of decompressive surgery, results from three European randomized controlled trials (DECIMAL, DESTINY, HAMLET) were pooled.**

Lancet Neurol. 2007 Mar;6(3):215-22.



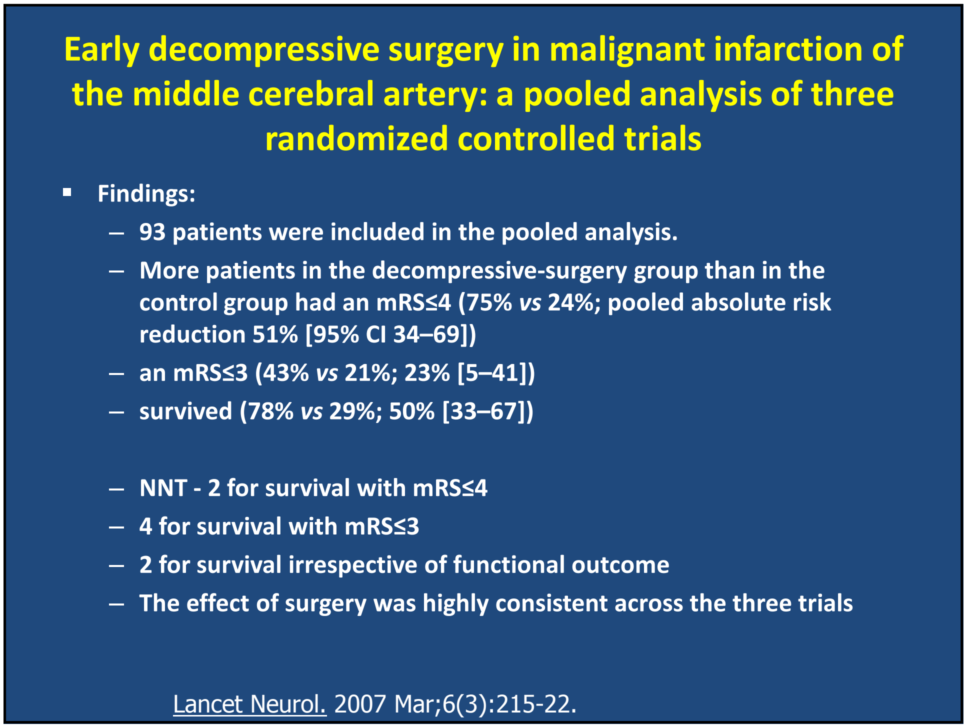
Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomized controlled trials

- 18 years and 60 years
- Space-occupying MCA infarction
- Treated within 48 h after stroke onset were pooled for analysis
- The protocol was designed prospectively

- The primary outcome measure
  - Modified Rankin scale (mRS) at 1 year
  - Favorable (0–4) and unfavourable (5 and death) outcome.

- Secondary outcome measures
  - Case fatality rate at 1 year and
  - mRS between 0–3 and 4 to death.

Lancet Neurol. 2007 Mar;6(3):215-22.

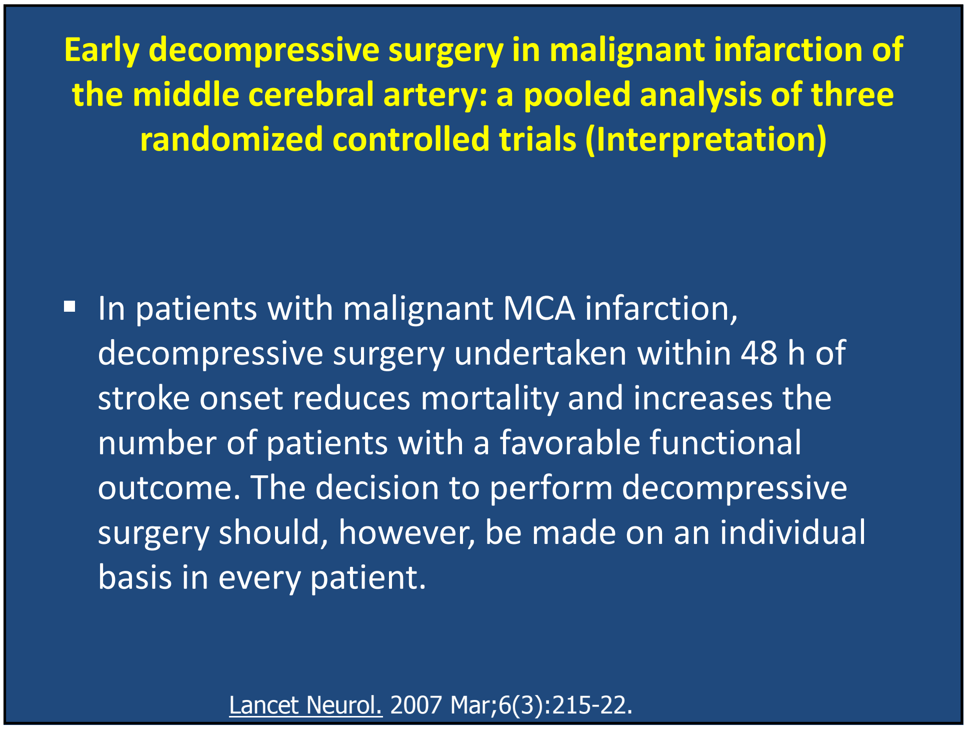


Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomized controlled trials

- Findings:
  - 93 patients were included in the pooled analysis.
  - More patients in the decompressive-surgery group than in the control group had an mRS≤4 (75% *vs* 24%; pooled absolute risk reduction 51% [95% CI 34–69])
  - an mRS≤3 (43% *vs* 21%; 23% [5–41])
  - survived (78% *vs* 29%; 50% [33–67])

  - NNT - 2 for survival with mRS≤4
  - 4 for survival with mRS≤3
  - 2 for survival irrespective of functional outcome
  - The effect of surgery was highly consistent across the three trials

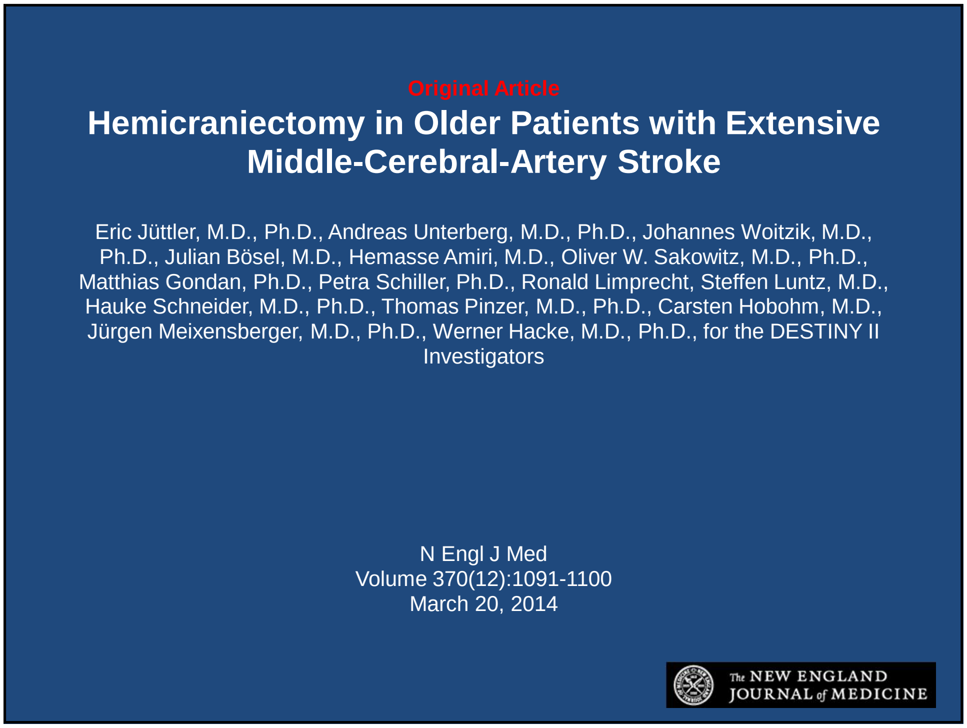
Lancet Neurol. 2007 Mar;6(3):215-22.



Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomized controlled trials (Interpretation)

- In patients with malignant MCA infarction, decompressive surgery undertaken within 48 h of stroke onset reduces mortality and increases the number of patients with a favorable functional outcome. The decision to perform decompressive surgery should, however, be made on an individual basis in every patient.

Lancet Neurol. 2007 Mar;6(3):215-22.



Original Article

Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke

Eric Jüttler, M.D., Ph.D., Andreas Unterberg, M.D., Ph.D., Johannes Woitzik, M.D., Ph.D., Julian Bösel, M.D., Hemasse Amiri, M.D., Oliver W. Sakowitz, M.D., Ph.D., Matthias Gondan, Ph.D., Petra Schiller, Ph.D., Ronald Limprecht, Steffen Luntz, M.D., Hauke Schneider, M.D., Ph.D., Thomas Pinzer, M.D., Ph.D., Carsten Hobohm, M.D., Jürgen Meixensberger, M.D., Ph.D., Werner Hacke, M.D., Ph.D., for the DESTINY II Investigators

N Engl J Med
Volume 370(12):1091-1100
March 20, 2014

The NEW ENGLAND JOURNAL of MEDICINE

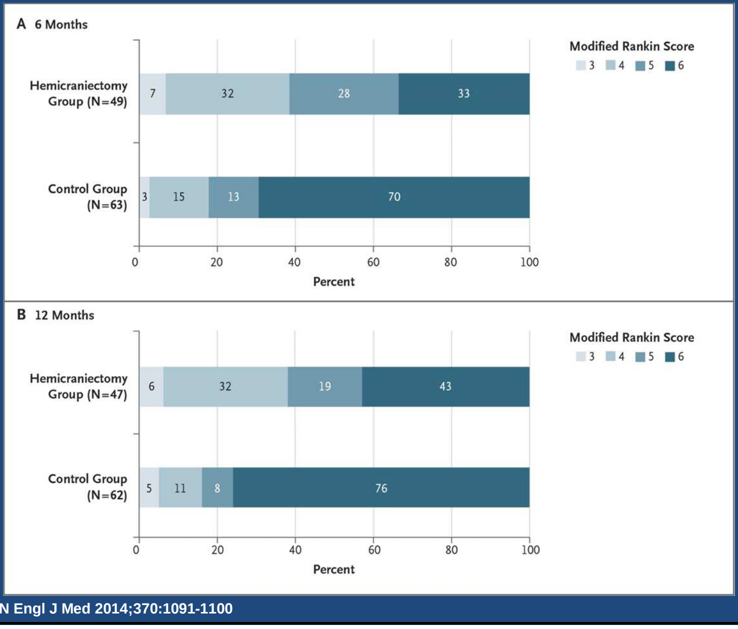
Study Overview

- In patients older than 60 years of age with extensive middle-cerebral-artery strokes, early hemicraniectomy improved survival as compared with treatment in the ICU alone.

- The majority of survivors had substantial disability and required assistance with most bodily needs.

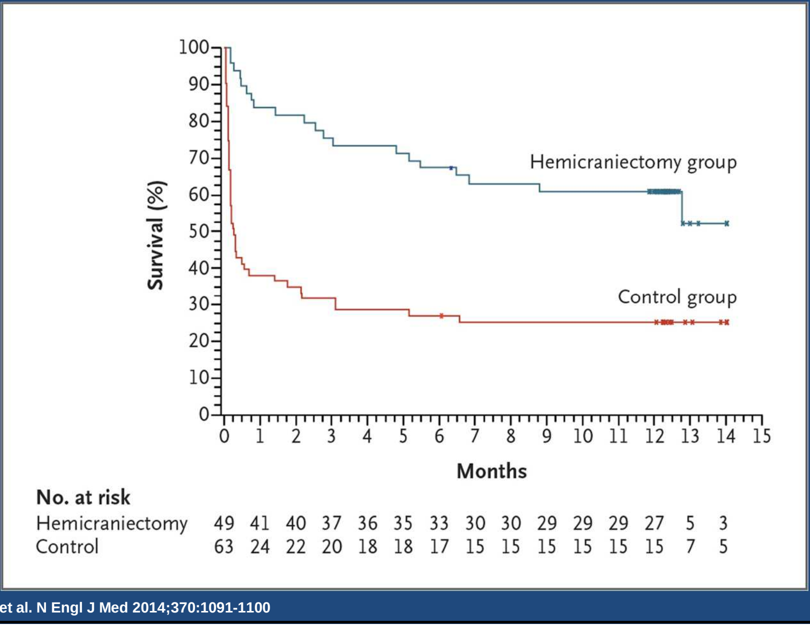
The NEW ENGLAND JOURNAL of MEDICINE

Functional Outcome after Hemicraniectomy and after Conservative Treatment Alone According to the Modified Rankin Score.



Jüttler E et al. N Engl J Med 2014;370:1091-1100

Kaplan–Meier Estimates of Survival in the Hemicraniectomy and Control Groups.



Jüttler E et al. N Engl J Med 2014;370:1091-1100

Causes of Death.

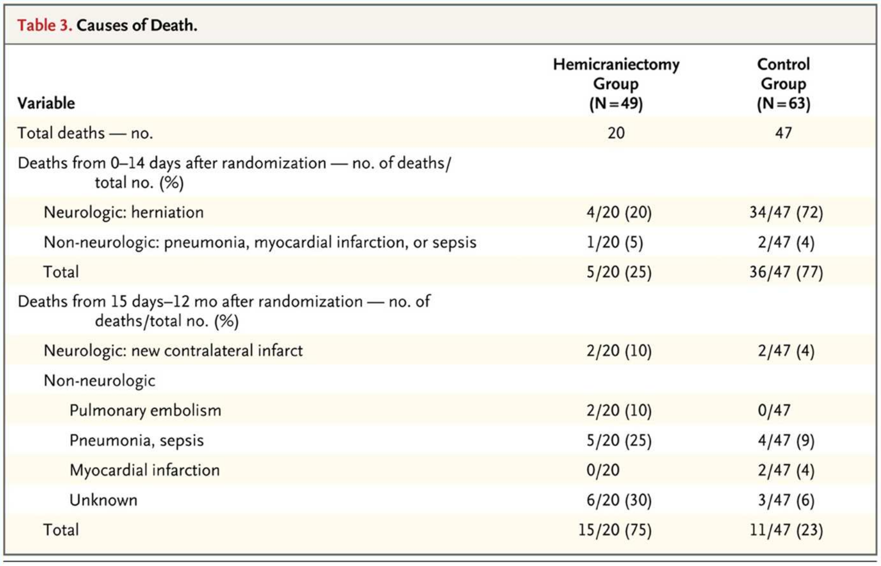
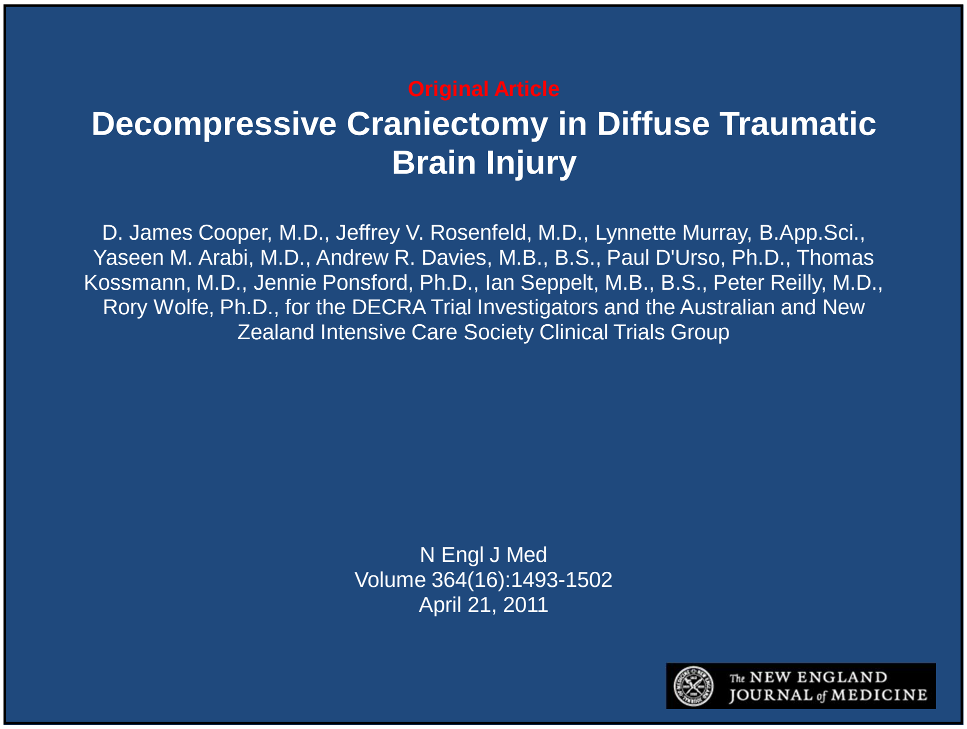


Table 3. Causes of Death.

Variable	Hemicraniectomy Group (N=49)	Control Group (N=63)
Total deaths — no.	20	47
Deaths from 0–14 days after randomization — no. of deaths/total no. (%)		
Neurologic: herniation	4/20 (20)	34/47 (72)
Non-neurologic: pneumonia, myocardial infarction, or sepsis	1/20 (5)	2/47 (4)
Total	5/20 (25)	36/47 (77)
Deaths from 15 days–12 mo after randomization — no. of deaths/total no. (%)		
Neurologic: new contralateral infarct	2/20 (10)	2/47 (4)
Non-neurologic		
Pulmonary embolism	2/20 (10)	0/47
Pneumonia, sepsis	5/20 (25)	4/47 (9)
Myocardial infarction	0/20	2/47 (4)
Unknown	6/20 (30)	3/47 (6)
Total	15/20 (75)	11/47 (23)

Jüttler E et al. N Engl J Med 2014;370:1091-1100



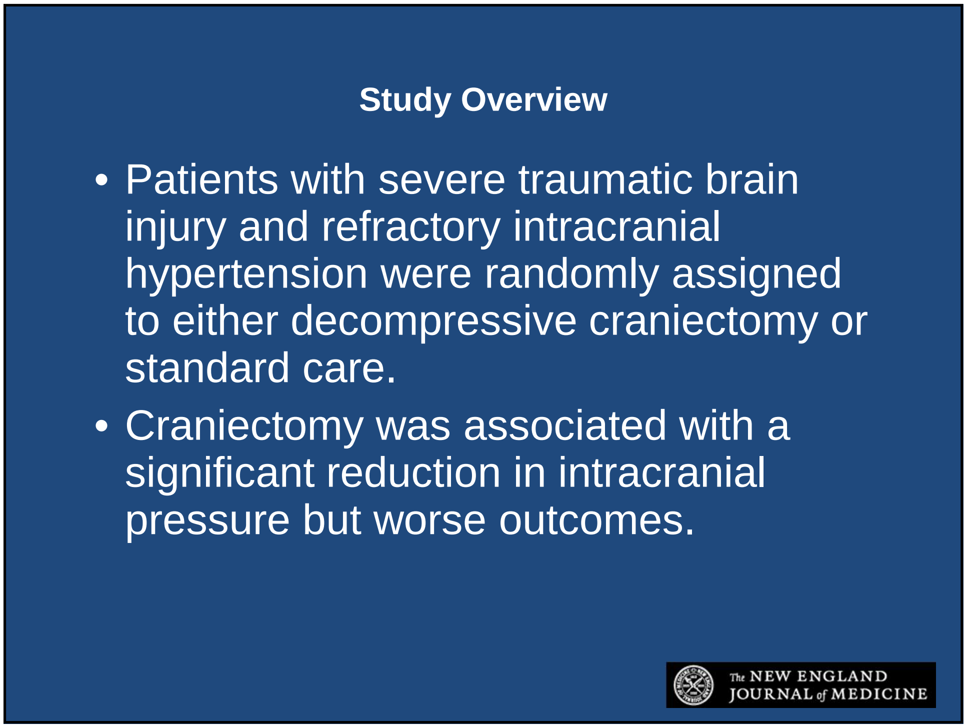
Original Article

Decompressive Craniectomy in Diffuse Traumatic Brain Injury

D. James Cooper, M.D., Jeffrey V. Rosenfeld, M.D., Lynnette Murray, B.App.Sci., Yaseen M. Arabi, M.D., Andrew R. Davies, M.B., B.S., Paul D'Urso, Ph.D., Thomas Kossmann, M.D., Jennie Ponsford, Ph.D., Ian Seppelt, M.B., B.S., Peter Reilly, M.D., Rory Wolfe, Ph.D., for the DECRA Trial Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group

N Engl J Med
Volume 364(16):1493-1502
April 21, 2011

The NEW ENGLAND JOURNAL of MEDICINE



Study Overview

- Patients with severe traumatic brain injury and refractory intracranial hypertension were randomly assigned to either decompressive craniectomy or standard care.
- Craniectomy was associated with a significant reduction in intracranial pressure but worse outcomes.

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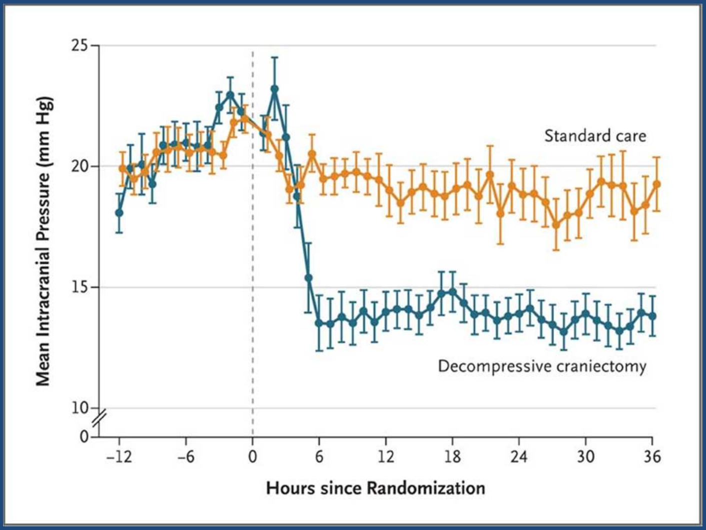
Intracranial Pressure before and after Randomization.



Cooper DJ et al. N Engl J Med 2011;364:1493-1502

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Conclusions

- In adults with severe diffuse traumatic brain injury and refractory intracranial hypertension, early bifrontotemporoparietal decompressive craniectomy decreased intracranial pressure and the length of stay in the ICU but was associated with more unfavorable outcomes.

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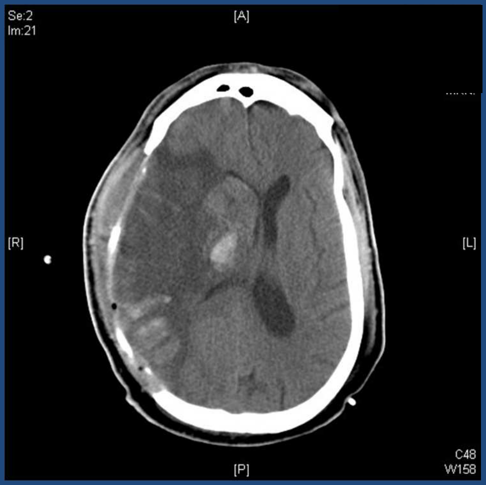
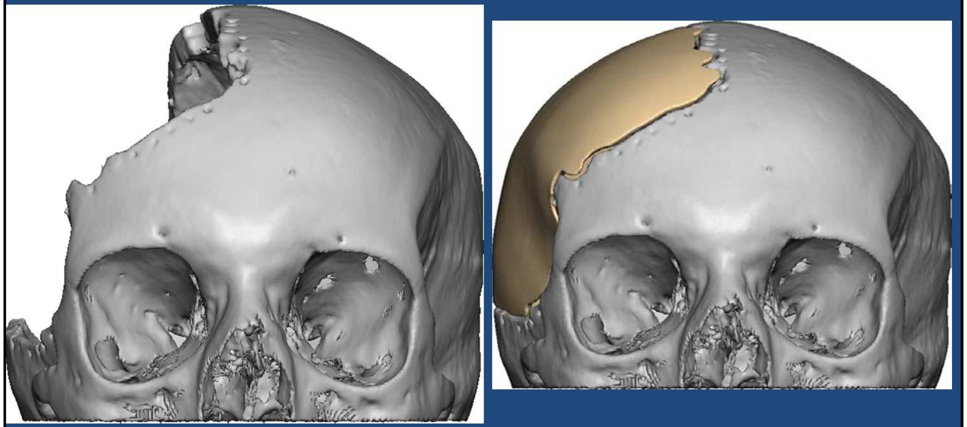
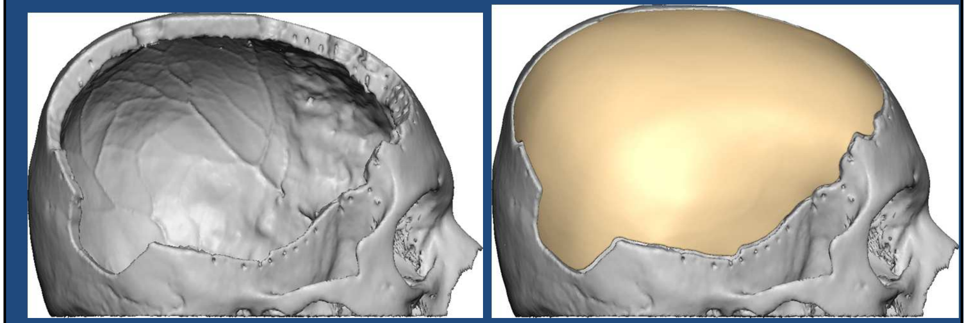
Decompression


Se:2
Im:21
[A]
[R]
[L]
[P]
C48
W158





Medical Management

General Measures

- Head position elevated 15-30^0 and in a neutral position avoid jugular compression
- Avoid hypotonic fluids
- Intubation to protect airway
- Osmolar therapy
- Glucose management
- Agitation, fever, and seizures should be treated
- Blood pressure management
- Neurosurgical consultation

Intracranial HTN Teatment Modalities with ICP monitoring

- Insert ICP monitor
- General goals: Maintain ICP < 20 mm Hg and CPP > 65 mm Hg
- For ICP > 20-25 mm Hg for > 5 minutes
  - Drain CSF via ventriculostomy
  - Elevate head of bed
  - Osmotherapy
  - Sedation, agitation and fever control
  - Hyperventilation
  - Pressor therapy to maintain MAP and ensure CPP
- For refractory intracranial HTN
  - Phenobarbital/Hypothermia/Decompressive craniotomy

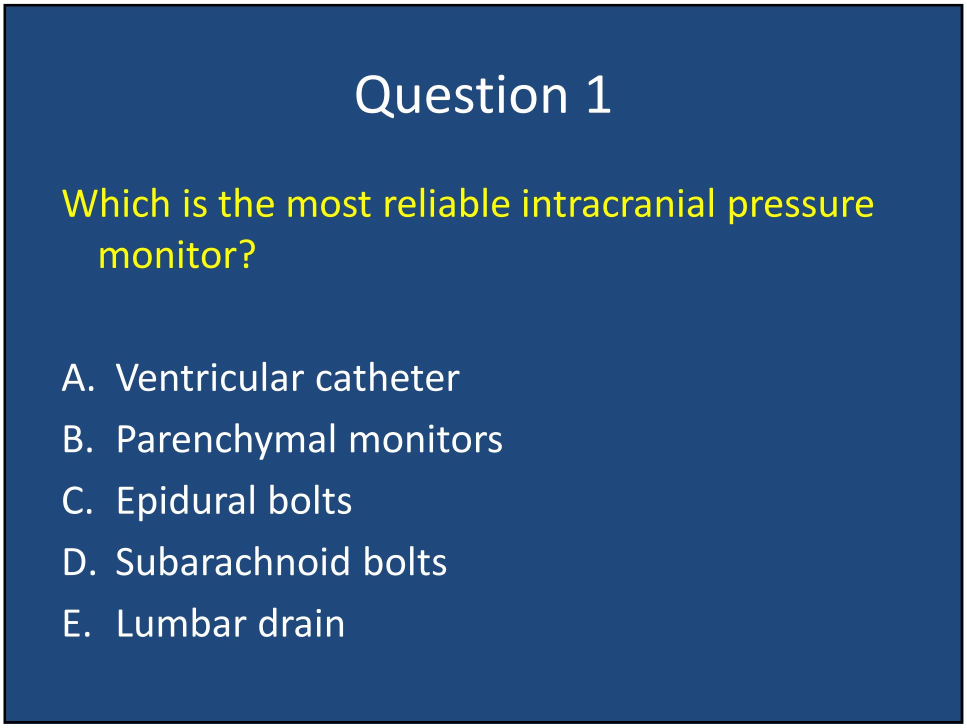
Summary

- Normal intracranial pressure
- Causes of intracranial HTN
- Herniation syndromes
- Medical management
- ICP monitoring
- Surgical management

Thank you

Galen V. Henderson, MD

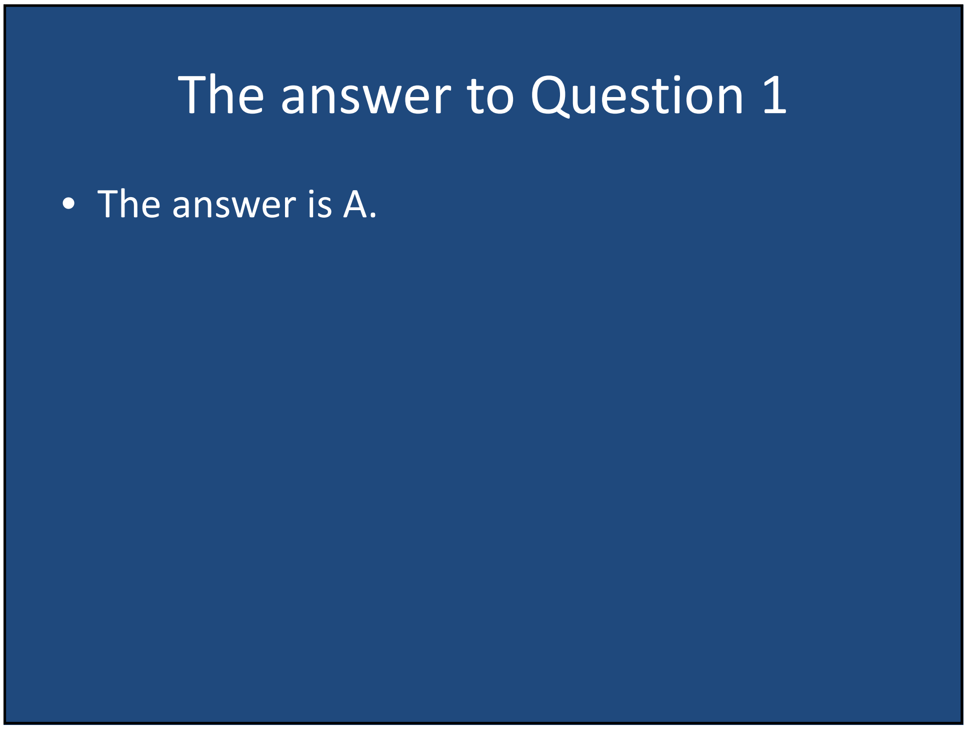
ghenderson@partners.org



Question 1

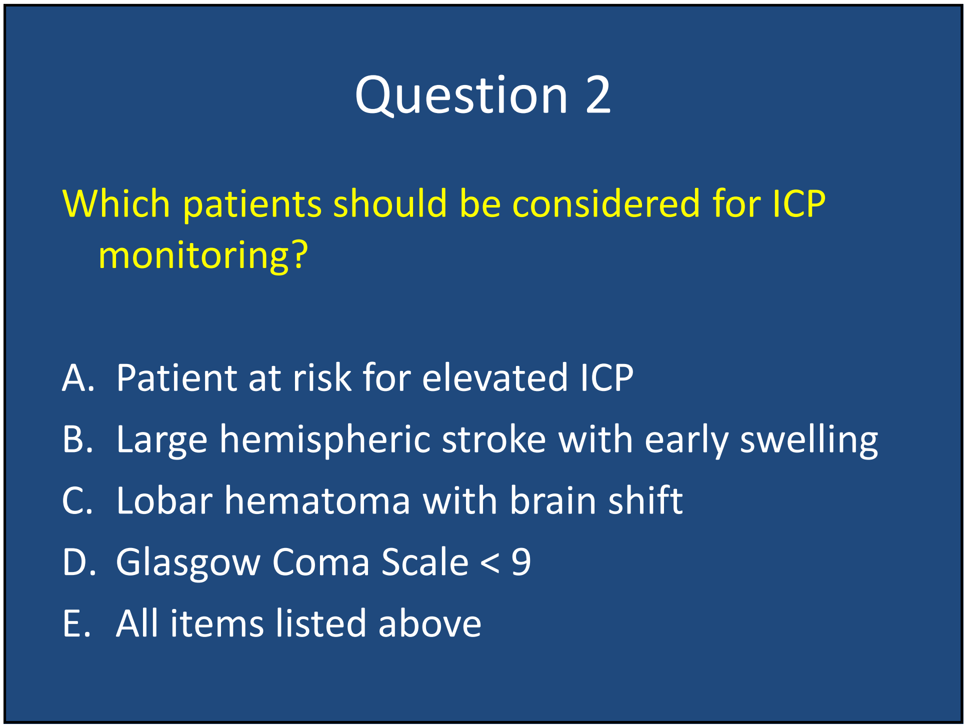
Which is the most reliable intracranial pressure monitor?

A. Ventricular catheter
B. Parenchymal monitors
C. Epidural bolts
D. Subarachnoid bolts
E. Lumbar drain



The answer to Question 1

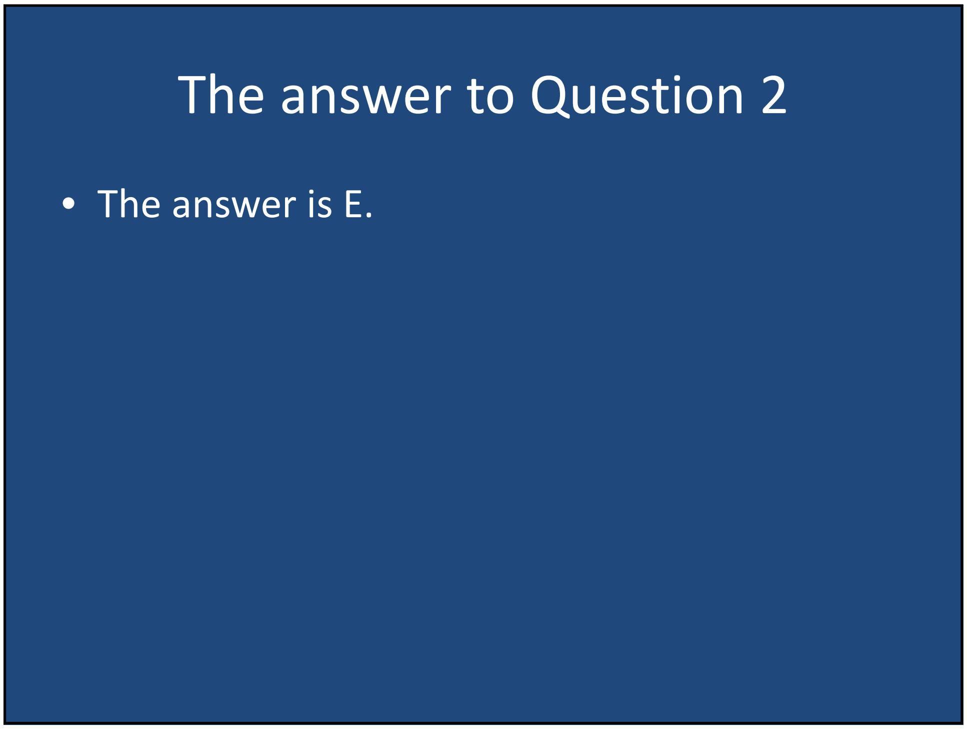
- The answer is A.



Question 2

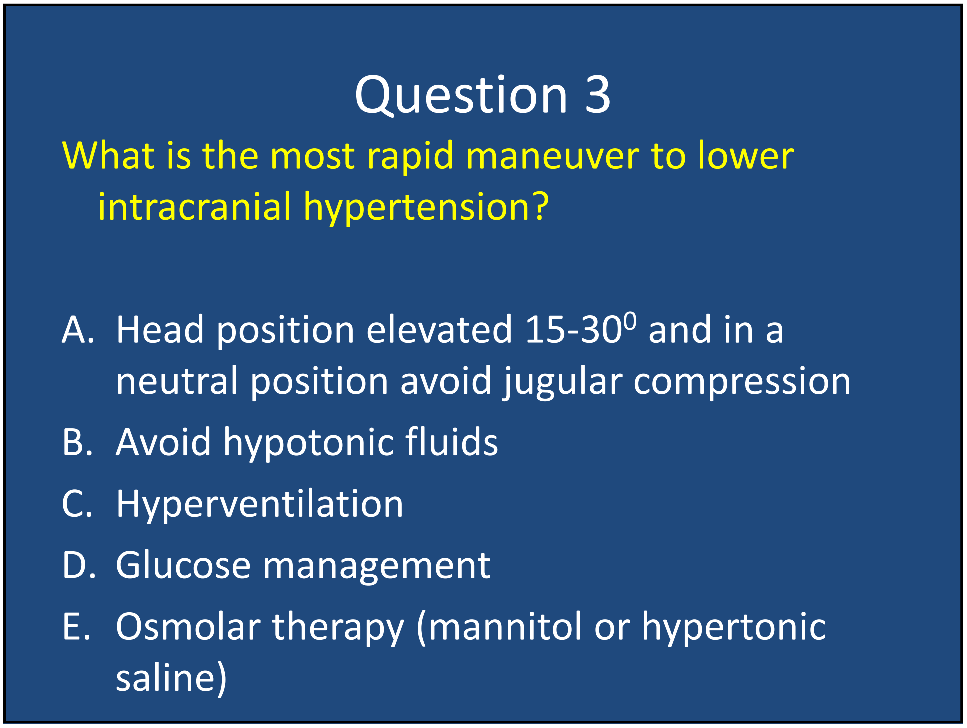
Which patients should be considered for ICP monitoring?

A. Patient at risk for elevated ICP
B. Large hemispheric stroke with early swelling
C. Lobar hematoma with brain shift
D. Glasgow Coma Scale < 9
E. All items listed above



The answer to Question 2

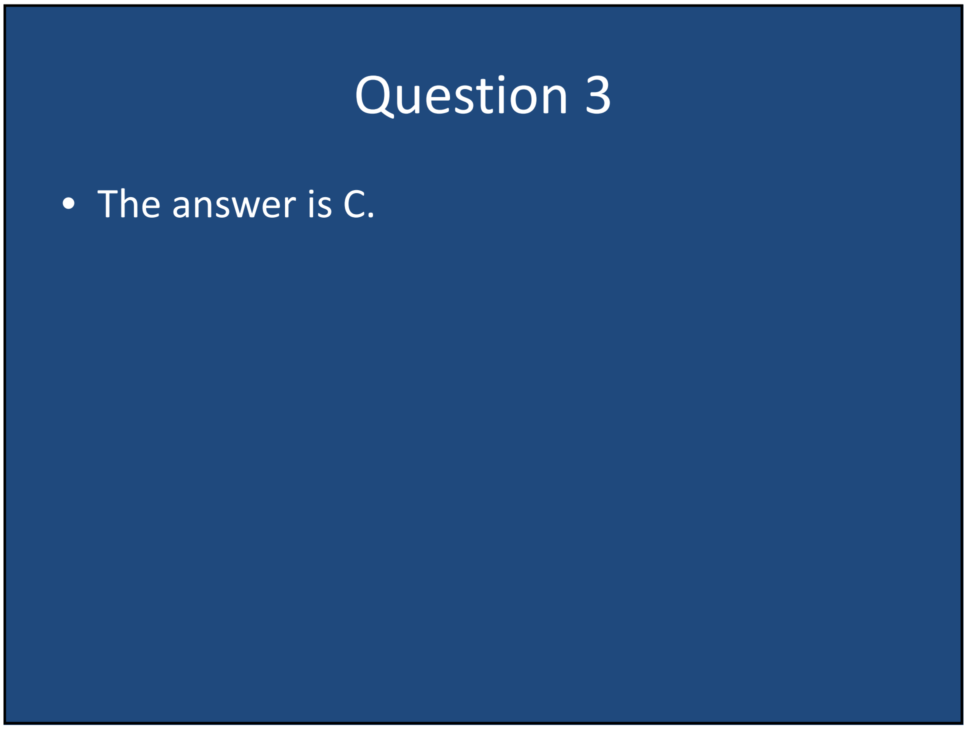
- The answer is E.



Question 3

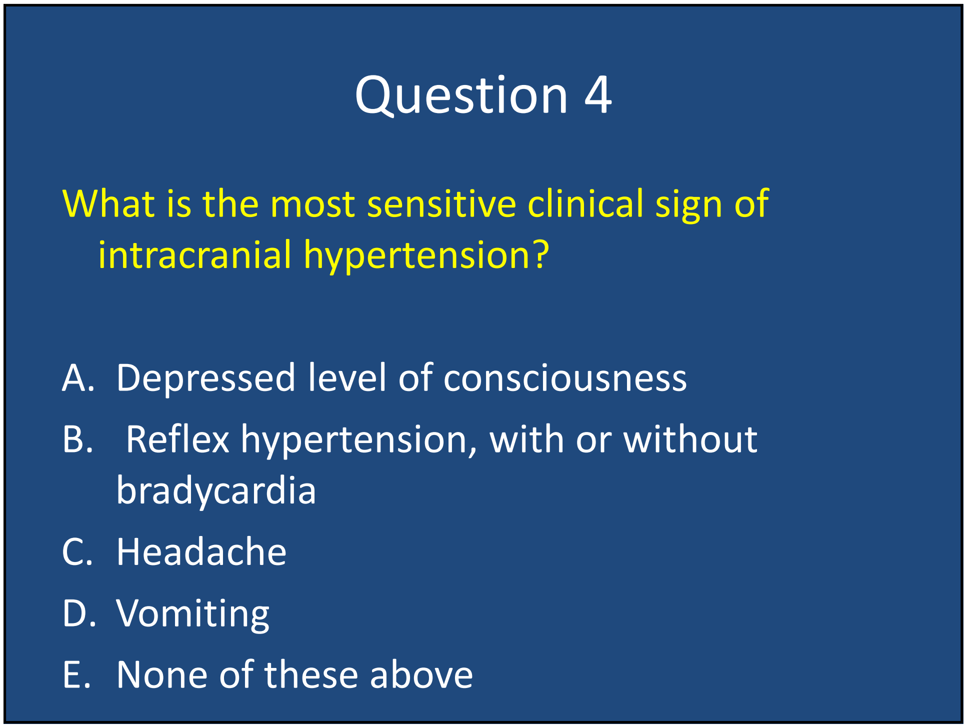
What is the most rapid maneuver to lower intracranial hypertension?

A. Head position elevated 15-30^0 and in a neutral position avoid jugular compression
B. Avoid hypotonic fluids
C. Hyperventilation
D. Glucose management
E. Osmolar therapy (mannitol or hypertonic saline)



Question 3

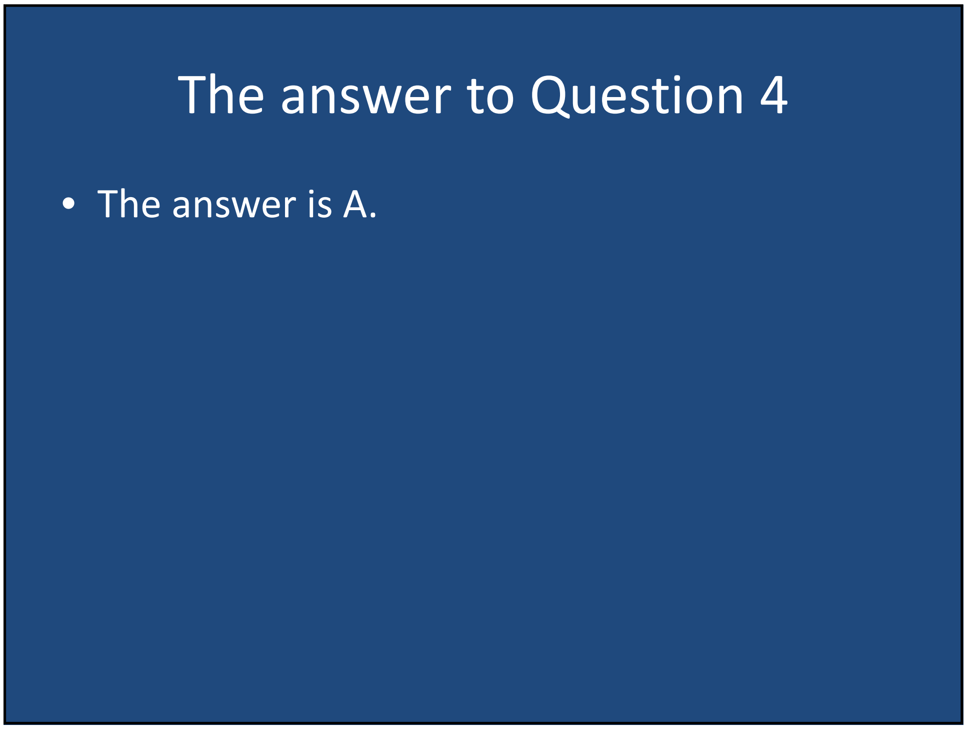
- The answer is C.



Question 4

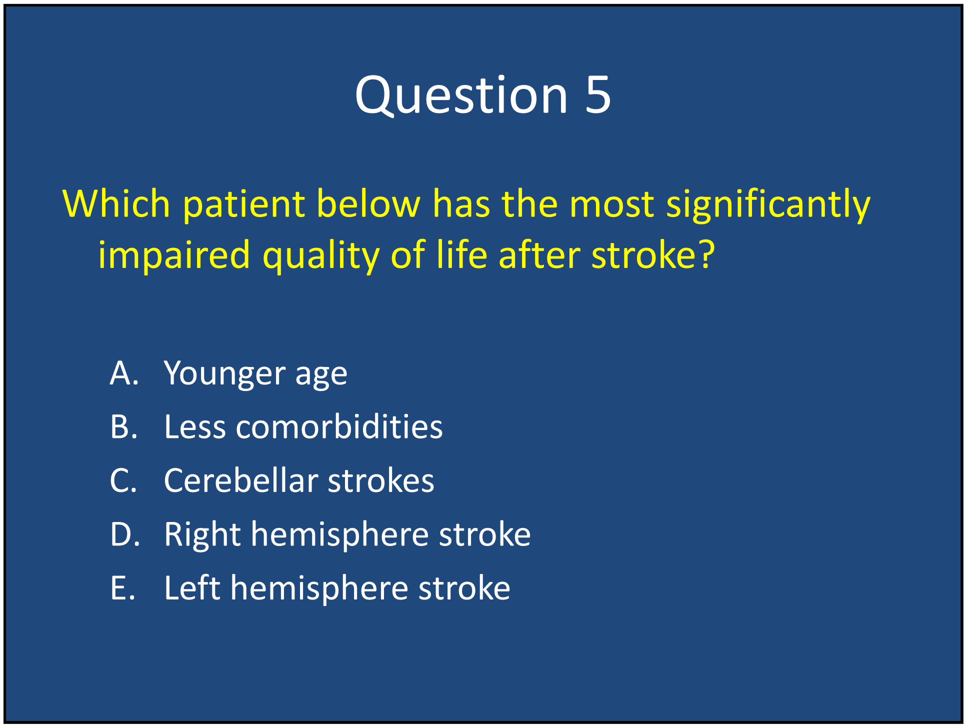
What is the most sensitive clinical sign of intracranial hypertension?

A. Depressed level of consciousness
B. Reflex hypertension, with or without bradycardia
C. Headache
D. Vomiting
E. None of these above



The answer to Question 4

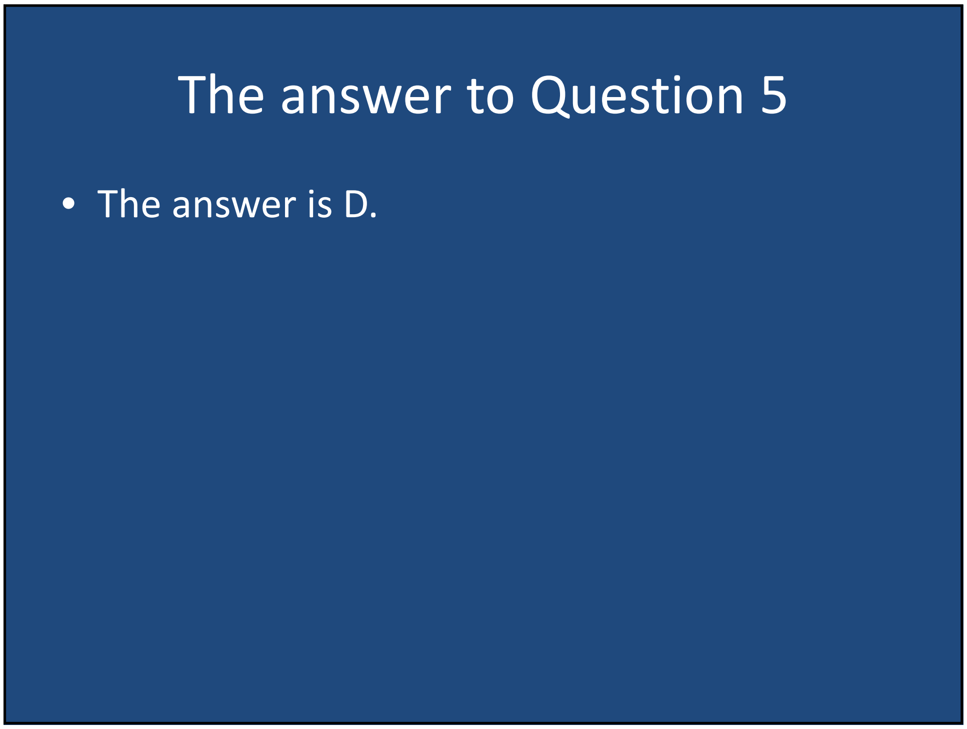
- The answer is A.



Question 5

Which patient below has the most significantly impaired quality of life after stroke?

A. Younger age
B. Less comorbidities
C. Cerebellar strokes
D. Right hemisphere stroke
E. Left hemisphere stroke



The answer to Question 5

- The answer is D.

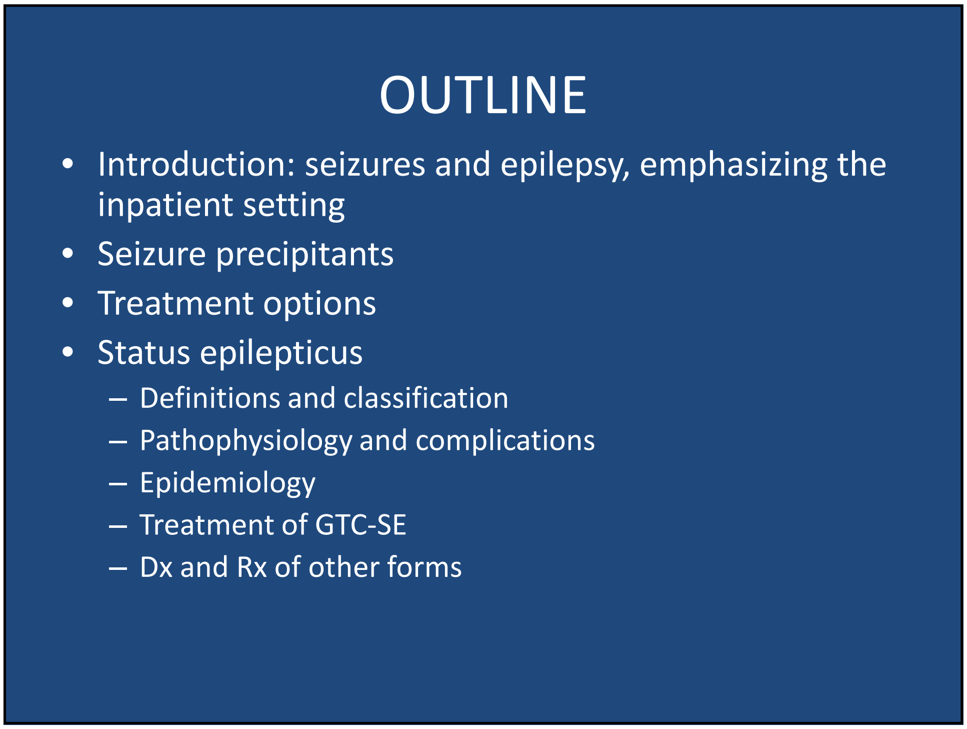
Seizures and Status Epilepticus

Galen V. Henderson, M.D.
Brigham and Women's Hospital
Director, Neuroscience ICU

Assistant Professor of Neurology
Harvard Medical School

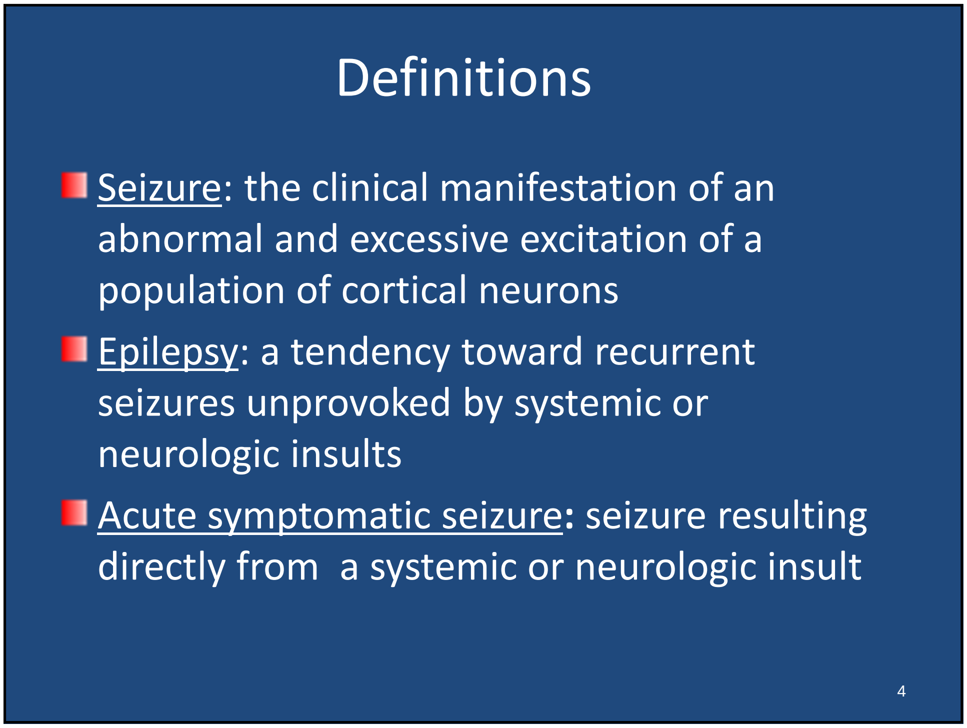
Disclosures

- I have no relationships with industry



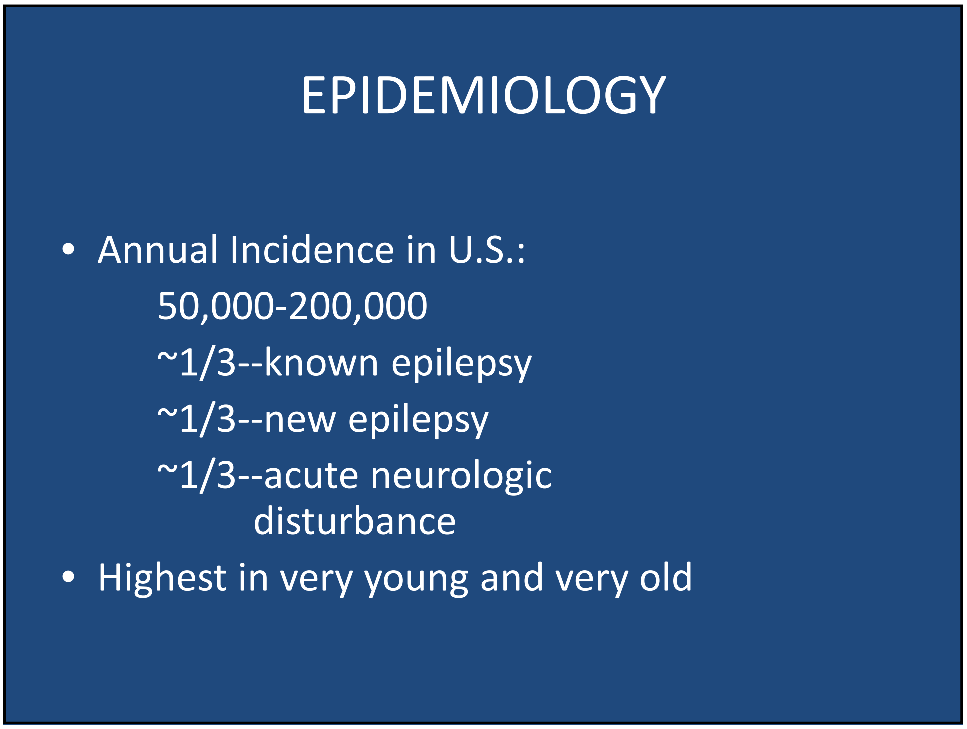
OUTLINE

- Introduction: seizures and epilepsy, emphasizing the inpatient setting
- Seizure precipitants
- Treatment options
- Status epilepticus
  - Definitions and classification
  - Pathophysiology and complications
  - Epidemiology
  - Treatment of GTC-SE
  - Dx and Rx of other forms



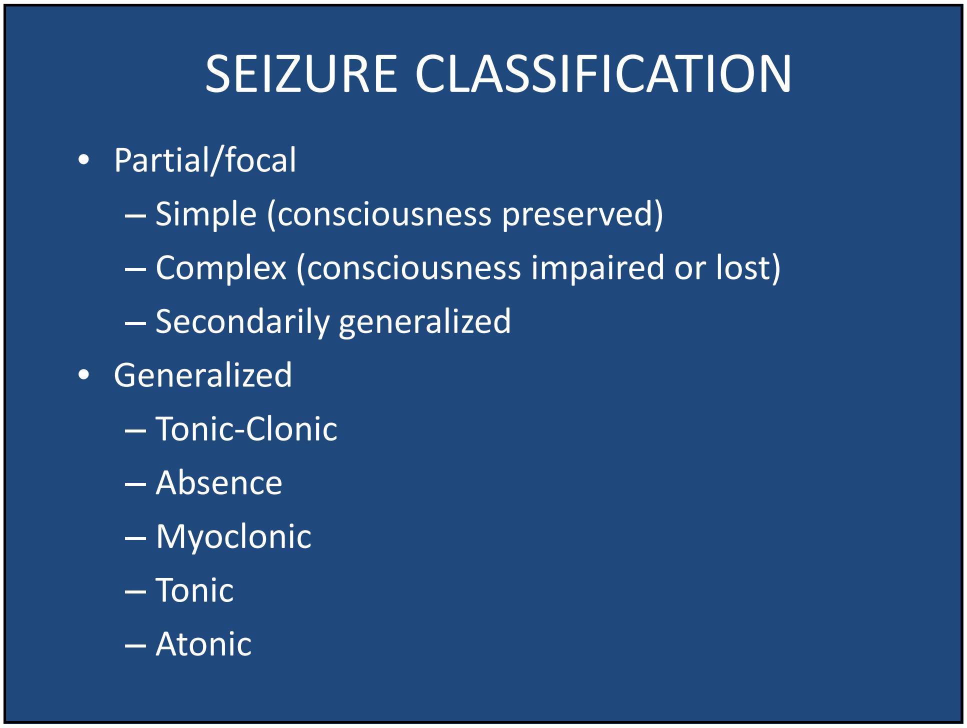
Definitions

- Seizure: the clinical manifestation of an abnormal and excessive excitation of a population of cortical neurons
- Epilepsy: a tendency toward recurrent seizures unprovoked by systemic or neurologic insults
- Acute symptomatic seizure**:** seizure resulting directly from a systemic or neurologic insult



EPIDEMIOLOGY

- Annual Incidence in U.S.:
  - 50,000-200,000
  - ~1/3--known epilepsy
  - ~1/3--new epilepsy
  - ~1/3--acute neurologic disturbance
- Highest in very young and very old



SEIZURE CLASSIFICATION

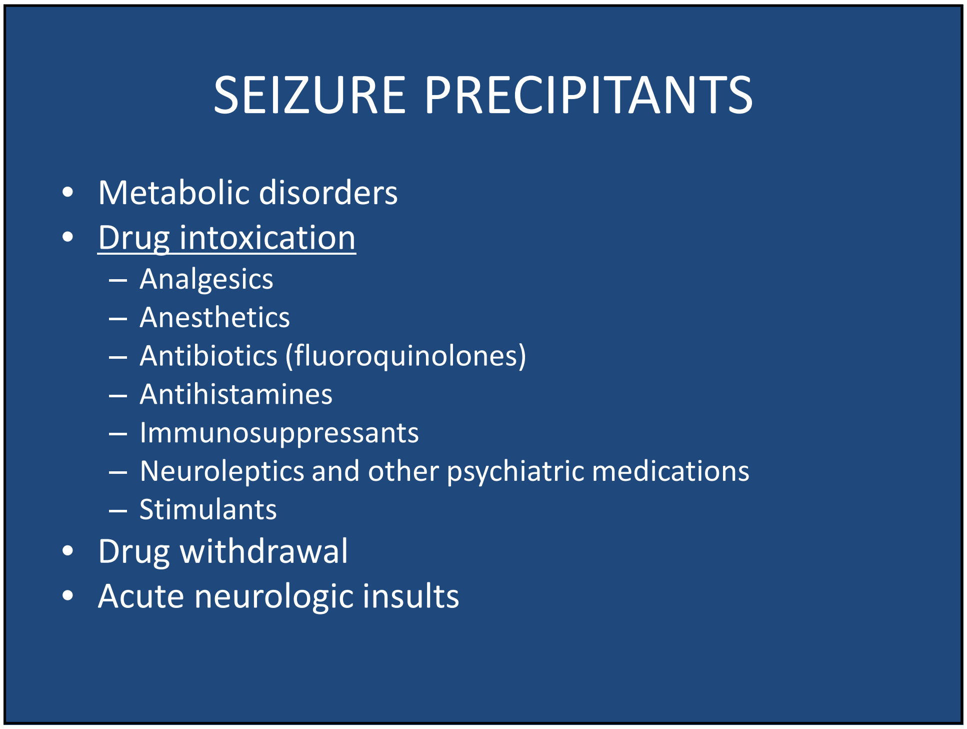
- Partial/focal
  - Simple (consciousness preserved)
  - Complex (consciousness impaired or lost)
  - Secondarily generalized
- Generalized
  - Tonic-Clonic
  - Absence
  - Myoclonic
  - Tonic
  - Atonic

ANTI-EPILEPTIC DRUG (AED) CONSIDERATIONS

- Spectrum of action
  - Narrow (partial and GTC)
  - Broad (partial, GTC, absence, myoclonic)
- Parenteral administration/loading options
- Pharmacokinetics and drug interactions
- Concomitant disease
- Likely adverse effects
  - Dose-related
  - Idiosyncratic
  - Chronic
- Efficacy
- Cost

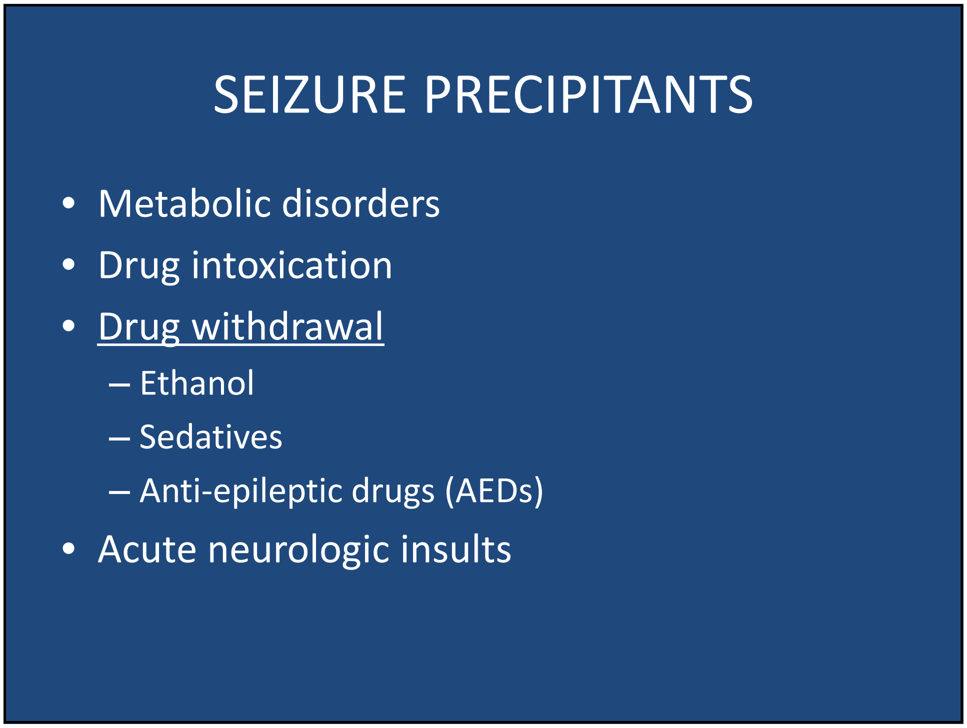
SEIZURE PRECIPITANTS

- Metabolic disorders
  - Hypoglycemia
  - Hyponatremia
  - Hypocalcemia
  - Hypomagnesemia
  - Hypoxemia
  - Renal failure
  - High fever, sleep deprivation
- Drug intoxication
- Drug withdrawal
- Acute neurologic insults



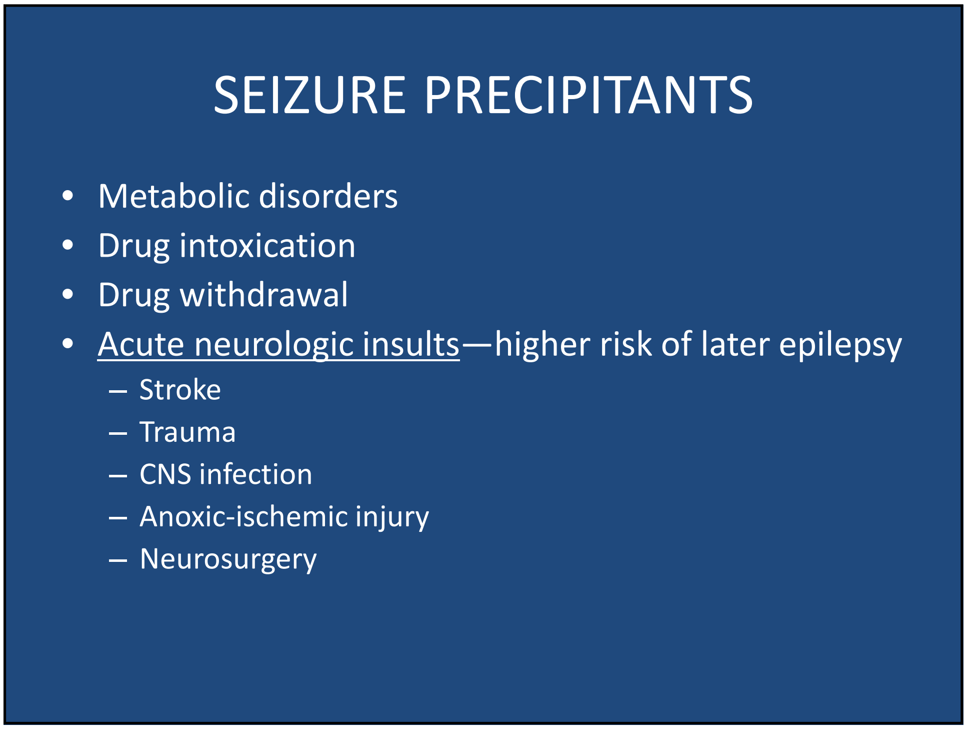
SEIZURE PRECIPITANTS

- Metabolic disorders
- Drug intoxication
  - Analgesics
  - Anesthetics
  - Antibiotics (fluoroquinolones)
  - Antihistamines
  - Immunosuppressants
  - Neuroleptics and other psychiatric medications
  - Stimulants
- Drug withdrawal
- Acute neurologic insults



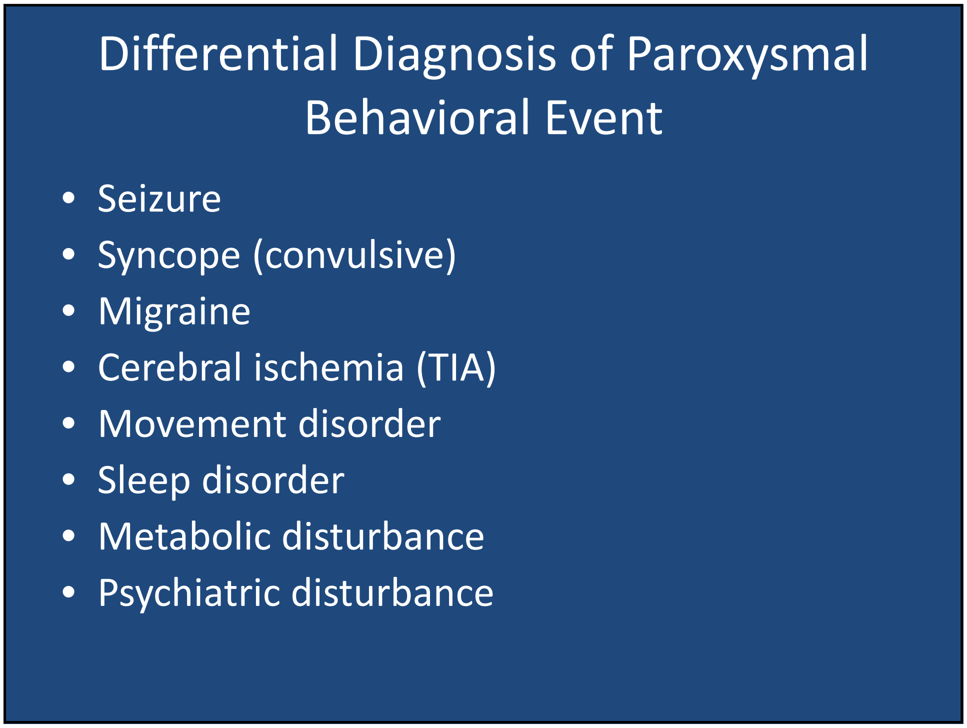
SEIZURE PRECIPITANTS

- Metabolic disorders
- Drug intoxication
- Drug withdrawal
  - Ethanol
  - Sedatives
  - Anti-epileptic drugs (AEDs)
- Acute neurologic insults



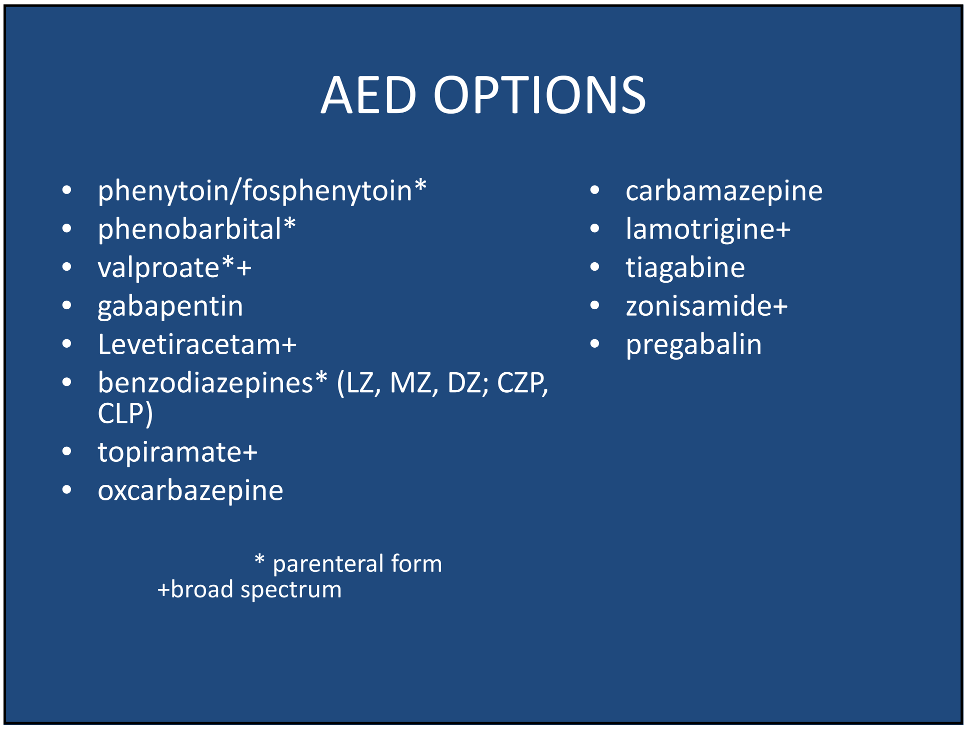
SEIZURE PRECIPITANTS

- Metabolic disorders
- Drug intoxication
- Drug withdrawal
- Acute neurologic insults—higher risk of later epilepsy
  - Stroke
  - Trauma
  - CNS infection
  - Anoxic-ischemic injury
  - Neurosurgery



Differential Diagnosis of Paroxysmal Behavioral Event

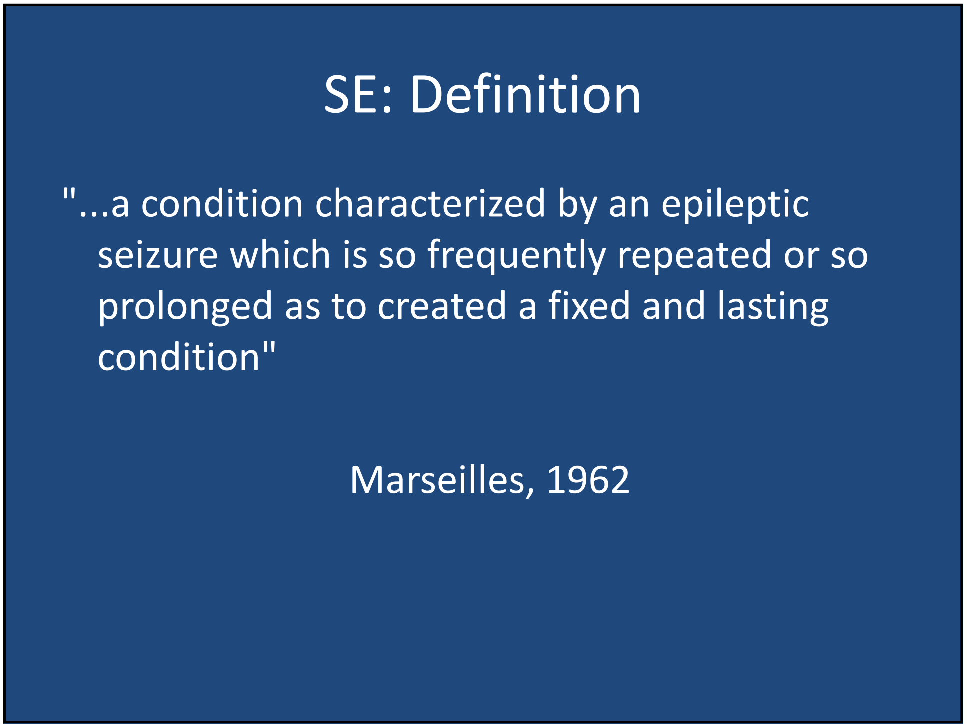
- Seizure
- Syncope (convulsive)
- Migraine
- Cerebral ischemia (TIA)
- Movement disorder
- Sleep disorder
- Metabolic disturbance
- Psychiatric disturbance



AED OPTIONS

- phenytoin/fosphenytoin*
- phenobarbital*
- valproate*+
- gabapentin
- Levetiracetam+
- benzodiazepines* (LZ, MZ, DZ; CZP, CLP)
- topiramate+
- oxcarbazepine
- carbamazepine
- lamotrigine+
- tiagabine
- zonisamide+
- pregabalin

* parenteral form
+broad spectrum



SE: Definition

"...a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to created a fixed and lasting condition"

Marseilles, 1962

Definition (cont.)

- Usual GTCS duration --1-2 min
- Official -- >5 min.

SE: Classification

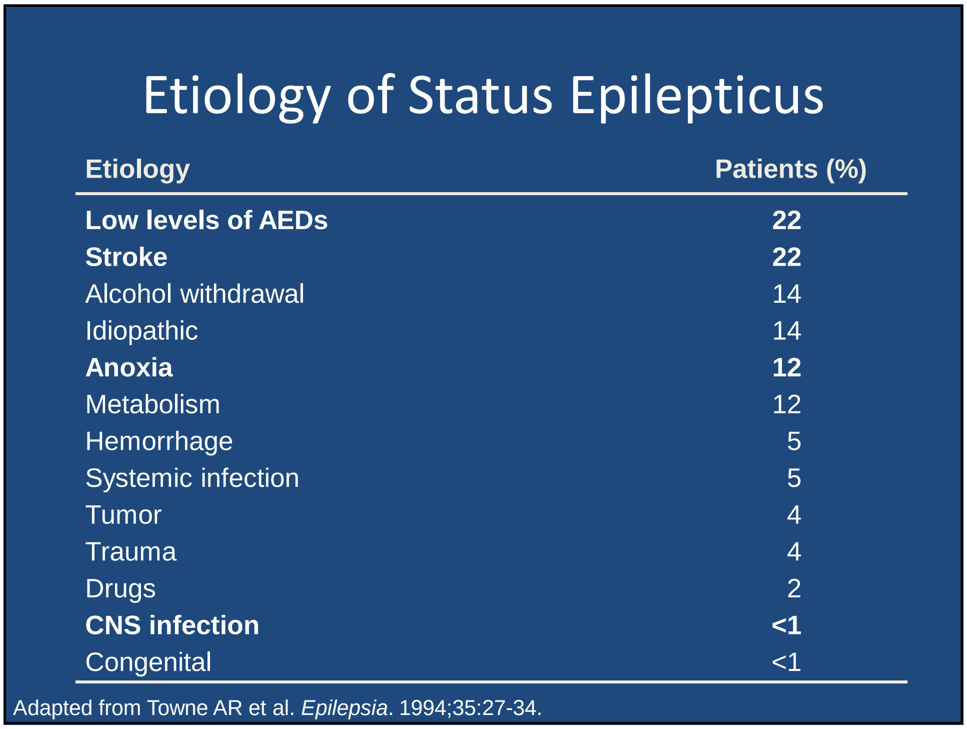
- Any seizure type can present as status epilepticus
- Convulsive vs. Nonconvulsive
- Partial vs. Generalized
- Main Types:
  - GCSE: generalized convulsive SE
  - NCSE: nonconvulsive SE
    - Generalized absence
    - Complex (simple) partial

DANGERS OF UNTREATED GCSE (increase after 30-60 min)

- SYSTEMIC:
  - Cardiovascular
  - Respiratory
  - Renal
  - Other (hyperthermia, acidosis, hyper/hypoglycemia)

DANGERS OF UNTREATED GCSE (increase after 30-60 min)

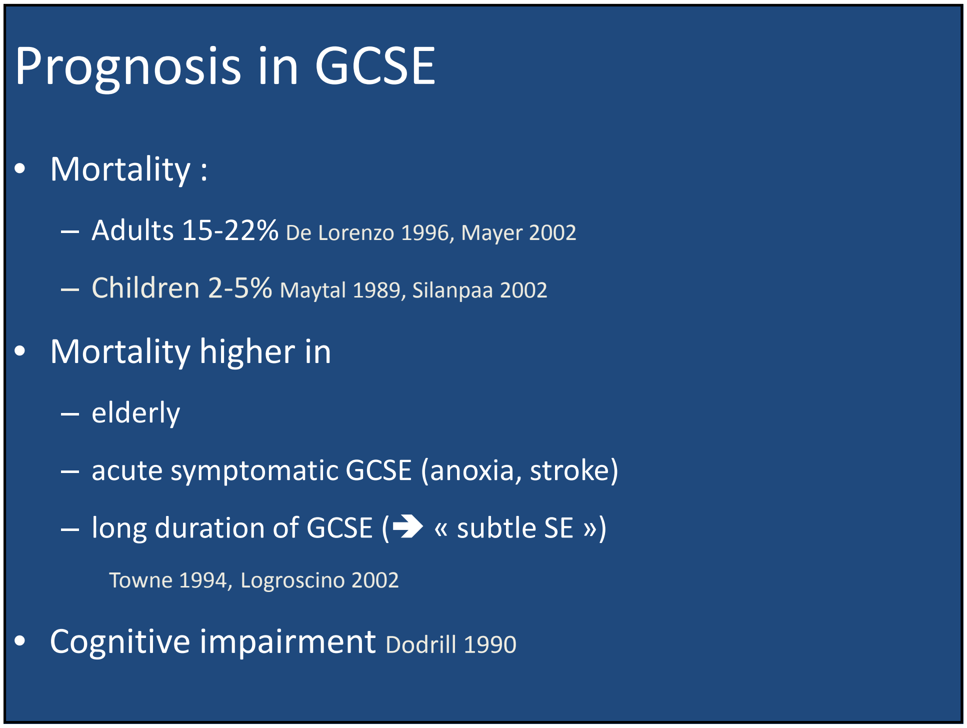
- NEUROLOGIC:
  - Cerebral edema
  - Neuronal death (cortex, hippocampus, thalamus, cerebellum, amygdala)
  - Morbidity among survivors
  - Attenuated but not eliminated, at least in animal models, by systemic support



Etiology of Status Epilepticus

Etiology	Patients (%)
Low levels of AEDs	**22**
Stroke	**22**
Alcohol withdrawal	14
Idiopathic	14
Anoxia	**12**
Metabolism	12
Hemorrhage	5
Systemic infection	5
Tumor	4
Trauma	4
Drugs	2
CNS infection	**<1**
Congenital	<1

Adapted from Towne AR et al. *Epilepsia*. 1994;35:27-34.

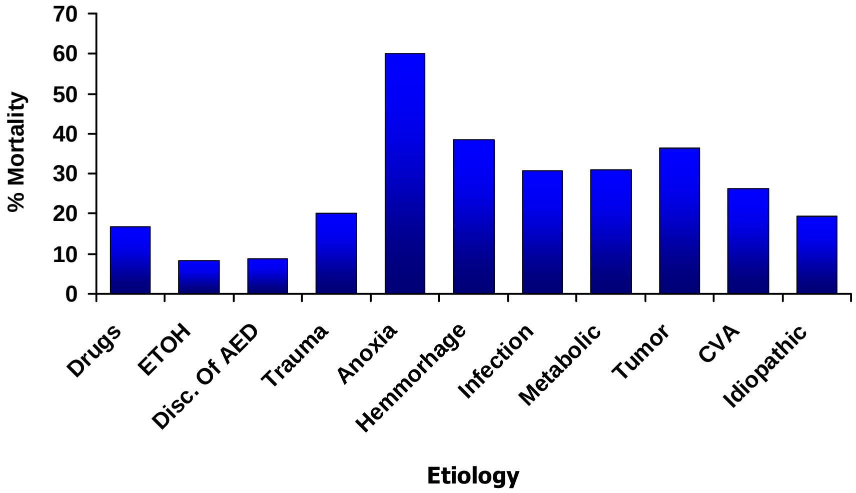


Prognosis in GCSE

- Mortality :
  - Adults 15-22% De Lorenzo 1996, Mayer 2002
  - Children 2-5% Maytal 1989, Silanpaa 2002
- Mortality higher in
  - elderly
  - acute symptomatic GCSE (anoxia, stroke)
  - long duration of GCSE (➔ « subtle SE »)

    Towne 1994, Logroscino 2002
- Cognitive impairment Dodrill 1990

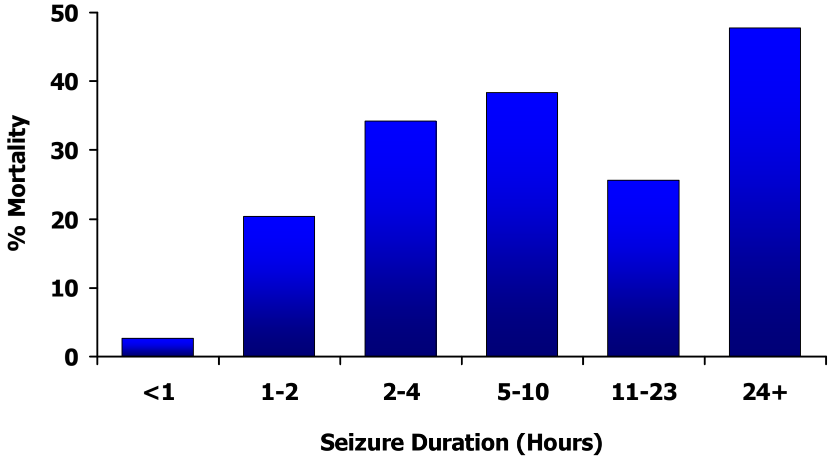
Mortality by Etiology in Status Epilepticus



Towne AR,et al 1994

Mortality by Seizure Duration in Status Epilepticus

(p=.003 for > or < 1 hr.)



Towne AR,et al 1994

Conclusions: SE Outcome
(Rossetti, JNNP 2006)

- Potentially fatal etiology, older age, stupor/coma ➔death in incident SE
  - First one is statistically most important
  - Last two are available at presentation
- Morbidity (mortality) greater in incident SE than in recurrent SE
  - Suggests that prognosis is more related to etiology than to SE per se

Score to Assess Mortality Risk (Rossetti, Neurology 2006)

	Features	Score 2
Consciousness:	Alert or somnolent/confused Stuporous or comatose	0 1
Seizure type:	SP or CP GC NCSEC	0 1 2
Age:	< 65 years ≥ 65 years	0 2
History of previous seizures:	Yes No	0 1
Total		0-6

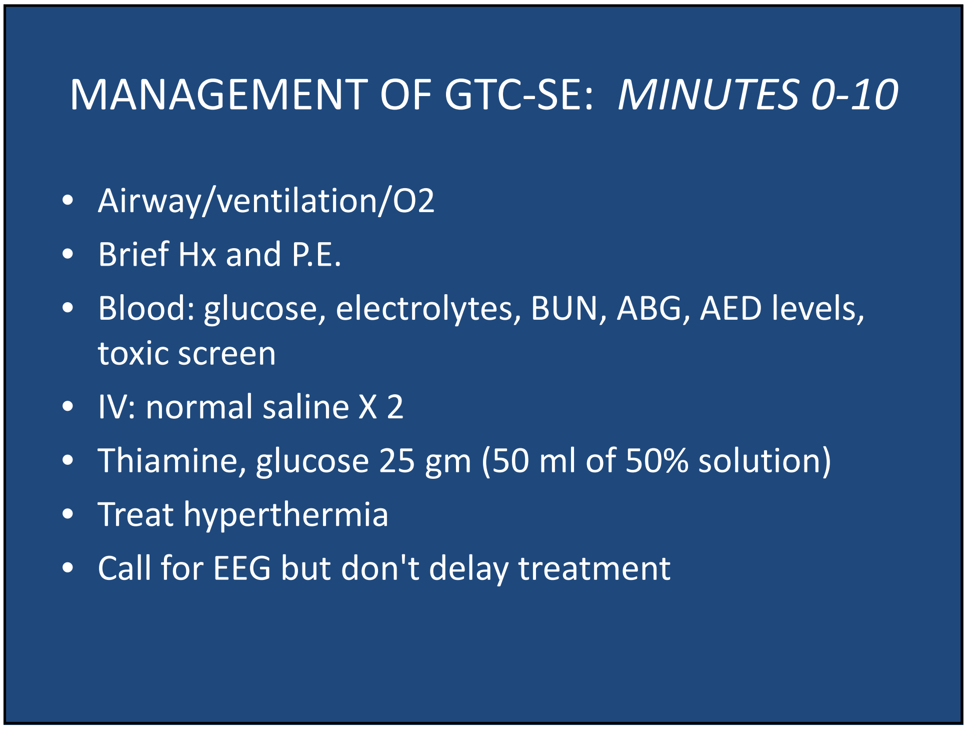
- SP = simple partial; CP = complex partial; GC = generalized convulsive; NCSEC = nonconvulsive status epilepticus with coma
- Score ≥ 3 to the prospective cohort results in the following: sensitivity = 1.000; specificity = 0.643; PPV = 0.375; NPV = 1.000; accuracy = 0.822. In other words, 6/6 subjects with fatal outcome, and 18/28 surviving patients were correctly identified.

DIAGNOSIS: THE KEY TO EARLY TREATMENT

- High index of suspicion
- If onset is unknown and a convulsion is witnessed after the patient reaches medical attention, SE should be assumed unless and until consciousness is regained

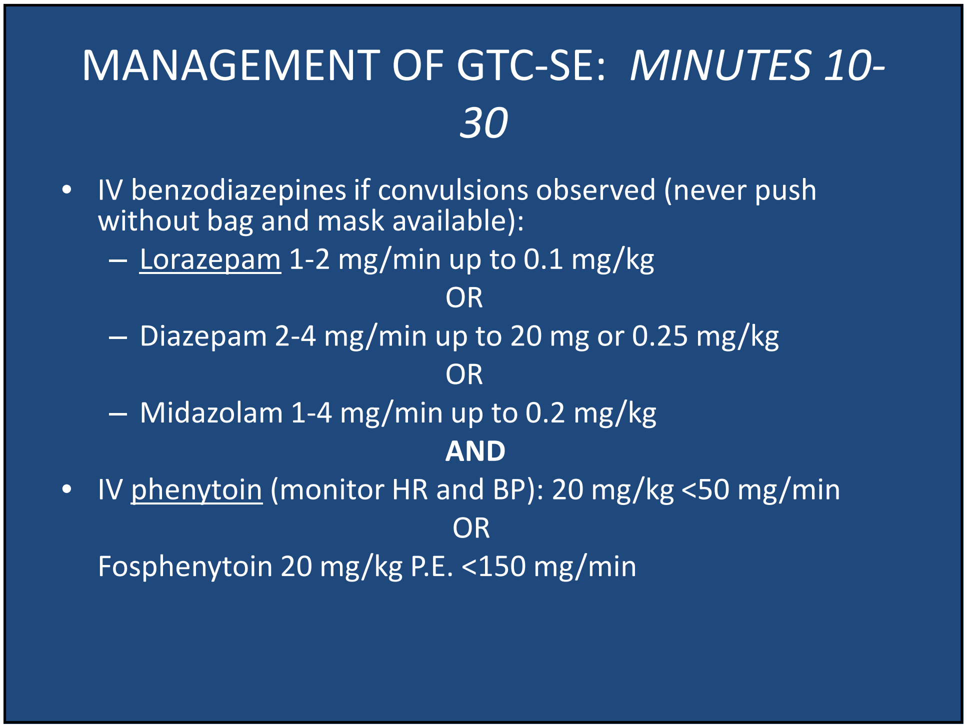
OUT-OF-HOSPITAL

- EMTs (Alldredge et al., 2001)
  - Lorazepam 2-4 mg (>) diazepam 5-10 mg >placebo
- Home (seizure clusters)
  - Rectal diazepam gel
  - Sublingual lorazepam
  - Buccal midazolam



MANAGEMENT OF GTC-SE: *MINUTES 0-10*

- Airway/ventilation/O2
- Brief Hx and P.E.
- Blood: glucose, electrolytes, BUN, ABG, AED levels, toxic screen
- IV: normal saline X 2
- Thiamine, glucose 25 gm (50 ml of 50% solution)
- Treat hyperthermia
- Call for EEG but don't delay treatment



MANAGEMENT OF GTC-SE: *MINUTES 10-30*

- IV benzodiazepines if convulsions observed (never push without bag and mask available):
  - Lorazepam 1-2 mg/min up to 0.1 mg/kg

    OR
  - Diazepam 2-4 mg/min up to 20 mg or 0.25 mg/kg

    OR
  - Midazolam 1-4 mg/min up to 0.2 mg/kg

AND

- IV phenytoin (monitor HR and BP): 20 mg/kg <50 mg/min

  OR

  Fosphenytoin 20 mg/kg P.E. <150 mg/min

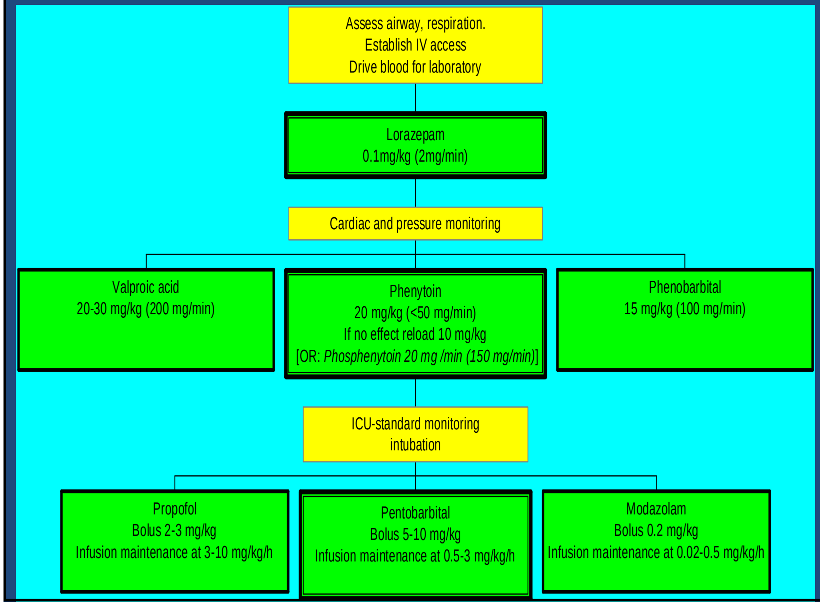
MANAGEMENT OF GTC-SE: *MINUTES 30-60 AND BEYOND*

- I.V. phenobarbital at 50 mg/min (monitor HR and BP) to 10-20 mg/kg
- I.V. valproate 20-30 mg/kg/min gm over 5-10 min
- I.V. levetiracetam 1 gm over 15 min, then 500 tid(?)
- Pentobarbital Coma:
  - 1) 5-10 mg/kg load at 25 mg/min to EEG burst-suppression or suppression of epileptiform activity
  - 2) 0.5-3 mg/kg/hr drip
  - 3) for breakthrough, bolus as needed and increase drip by 0.5-1.0 mg/kg/hr
  - 4) for hypotension, slow or stop drip; give fluids, pressors as needed

DRUG-INDUCED COMA (cont.)

- Midazolam
  - 0.20 mg/kg load
  - 0.05-0.50 mg/kg/hr infusion
- Propofol
  - 1-3 mg/kg boluses over 5 min
  - 2-5 mg/kg/hr, or higher
  - Benzodiazepines may potentiate (Rossetti, 2004)

Pharmacological treatment of generalized convulsive status epilepticus



Assess airway, respiration.
Establish IV access
Drive blood for laboratory

Lorazepam
0.1mg/kg (2mg/min)

< 5min

Cardiac and pressure monitoring

Valproic acid
20-30 mg/kg (200 mg/min)

Phenytoin
20 mg/kg (<50 mg/min)
If no effect reload 10 mg/kg
[OR: *Phosphenytoin 20 mg /min (150 mg/min)*]

Phenobarbital
15 mg/kg (100 mg/min)

< 10min

ICU-standard monitoring
intubation

Propofol
Bolus 2-3 mg/kg
Infusion maintenance at 3-10 mg/kg/h

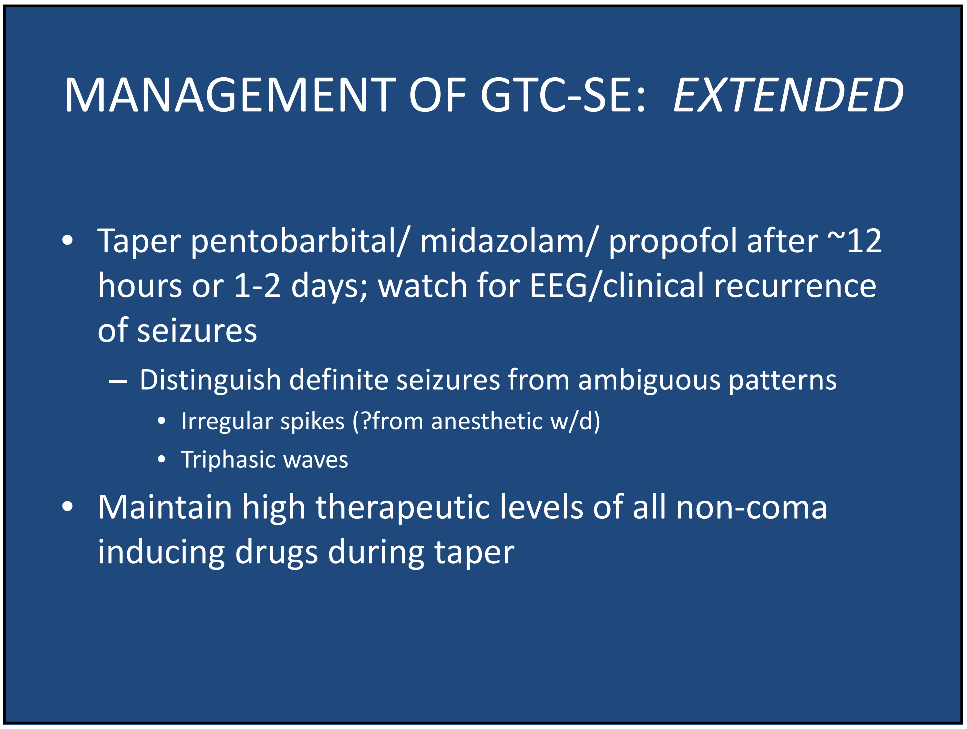
Pentobarbital
Bolus 5-10 mg/kg
Infusion maintenance at 0.5-3 mg/kg/h

Modazolam
Bolus 0.2 mg/kg
Infusion maintenance at 0.02-0.5 mg/kg/h

< 50 min

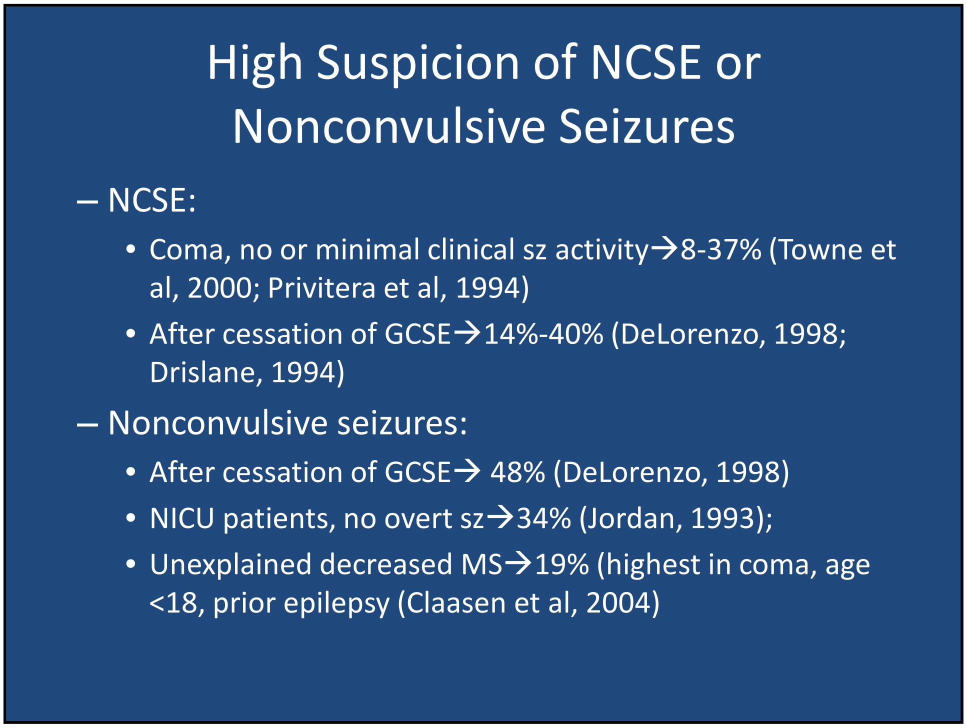
DRUG COMA (cont.)

- Endpoint:
  - Cessation of clinical seizures
  - Cessation of electrographic seizures
  - ?Cessation of discharges
  - ?Burst-suppression (e.g, 5-15 sec suppressions)
  - ?Complete suppression (Krishnamurthy and Drislane, 1999)



MANAGEMENT OF GTC-SE: *EXTENDED*

- Taper pentobarbital/ midazolam/ propofol after ~12 hours or 1-2 days; watch for EEG/clinical recurrence of seizures
  - Distinguish definite seizures from ambiguous patterns
    - Irregular spikes (?from anesthetic w/d)
    - Triphasic waves
- Maintain high therapeutic levels of all non-coma inducing drugs during taper



High Suspicion of NCSE or Nonconvulsive Seizures

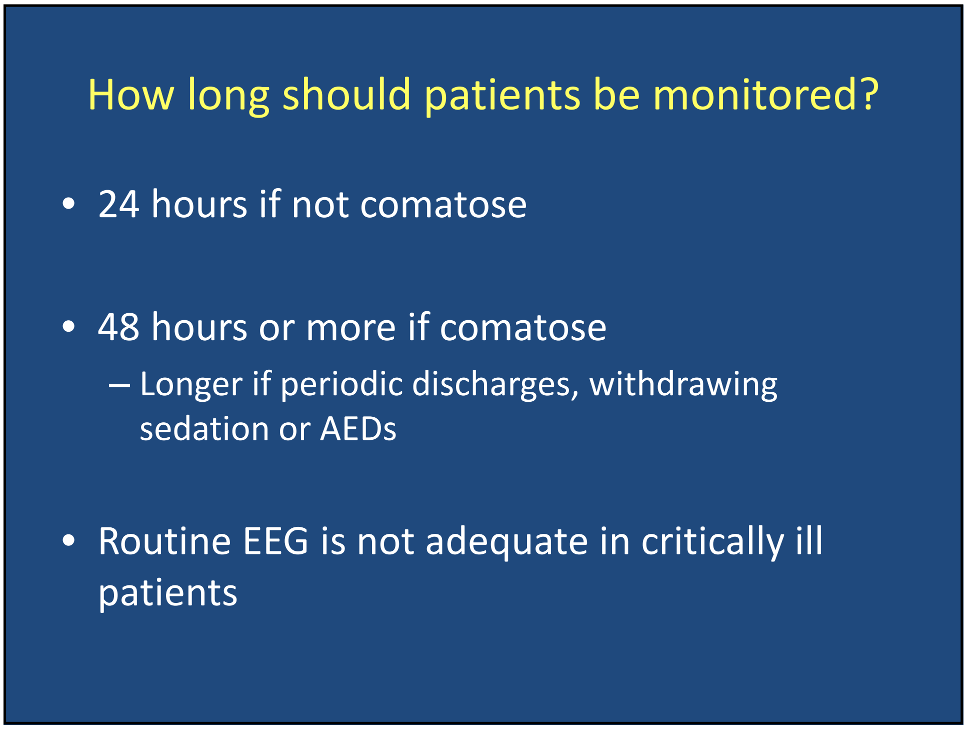
- NCSE:
  - Coma, no or minimal clinical sz activity→8-37% (Towne et al, 2000; Privitera et al, 1994)
  - After cessation of GCSE→14%-40% (DeLorenzo, 1998; Drislane, 1994)
- Nonconvulsive seizures:
  - After cessation of GCSE→ 48% (DeLorenzo, 1998)
  - NICU patients, no overt sz→34% (Jordan, 1993);
  - Unexplained decreased MS→19% (highest in coma, age <18, prior epilepsy (Claasen et al, 2004)

Evidence that seizures, including nonconvulsive ones, are causing further harm

- Status after stroke leads to 3X mortality, indep of ischemic stroke size or location (Waterhouse ' 98)
- Duration of seizure and delay to diagnosis are independent predictors of outcome in NCSE (Young '96) and CSE (Treiman ' 98)
- Case reports of prolonged nonconvulsive seizures without acute brain injury and permanent CNS injury/worsening
- Highest NSE is in those w/ acute brain injury + szs; szs alone can cause elevated NSE (DeGiorgio ' 95 + '99)

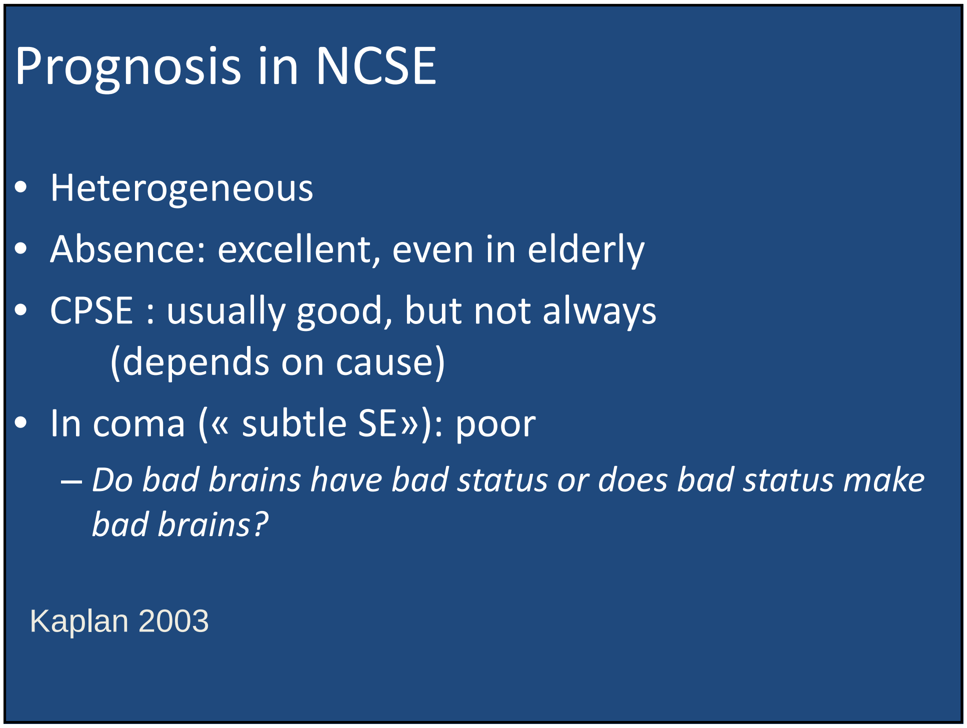
Evidence that seizures, including nonconvulsive ones, are causing further harm, cont' d

- In patients with ICH, nonconvulsive szs lead to more mass effect and shift Vespa 2003
- In animal models of acute stroke, NCSzs are associated with significant greater mortality and trend towards bigger infarcts. Williams AJ 2004



How long should patients be monitored?

- 24 hours if not comatose
- 48 hours or more if comatose
  - Longer if periodic discharges, withdrawing sedation or AEDs
- Routine EEG is not adequate in critically ill patients



Prognosis in NCSE

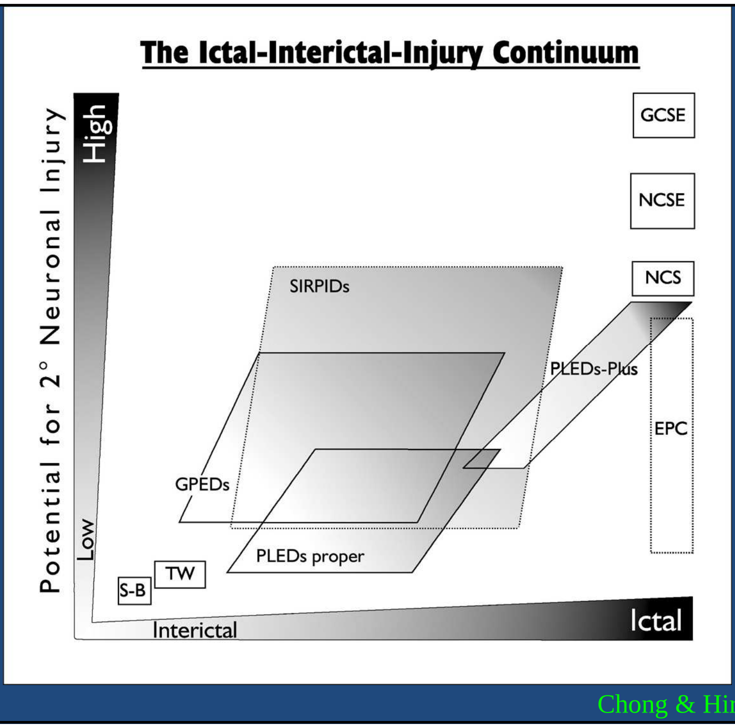
- Heterogeneous
- Absence: excellent, even in elderly
- CPSE : usually good, but not always
  (depends on cause)
- In coma (« subtle SE»): poor
  - *Do bad brains have bad status or does bad status make bad brains?*

Kaplan 2003

Why perform cVEEG in ICUs?

- To detect seizures:
  - Often subclinical and intermittent in ICUs

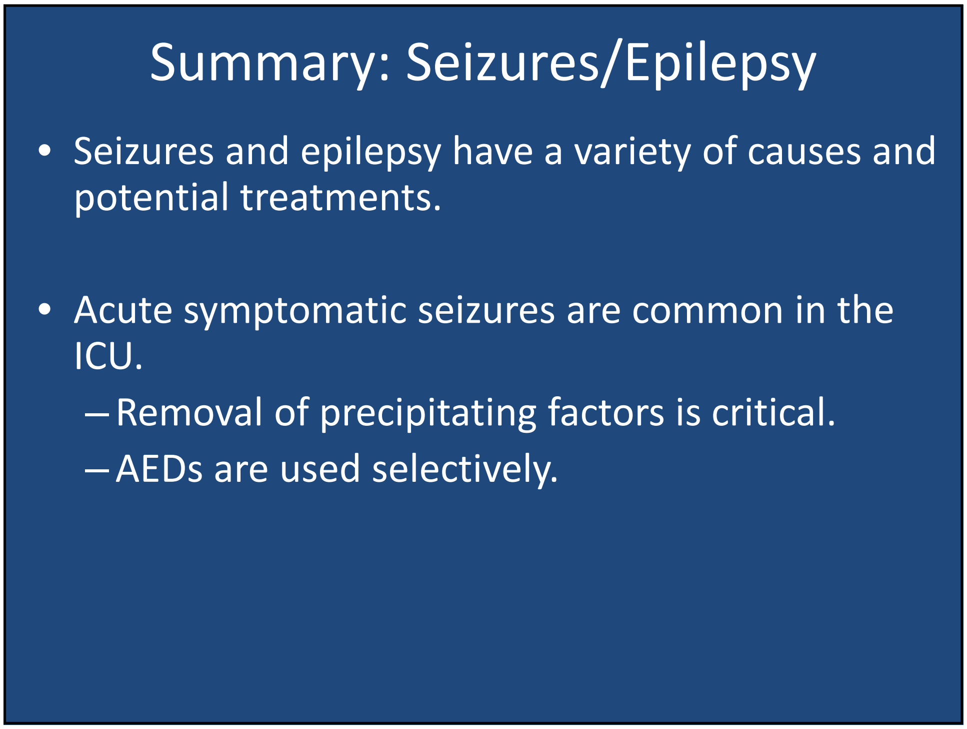
- Defining nature of spells, including autonomic
- Quantifying seizures
- Detecting hypoxia/ischemia
- Prognostication
- Other



The Ictal-Interictal-Injury Continuum

Potential for 2° Neuronal Injury
High
Low
GCSE
NCSE
NCS
SIRPIDs
PLEDs-Plus
EPC
GPEDs
PLEDs proper
TW
S-B
Interictal
Ictal

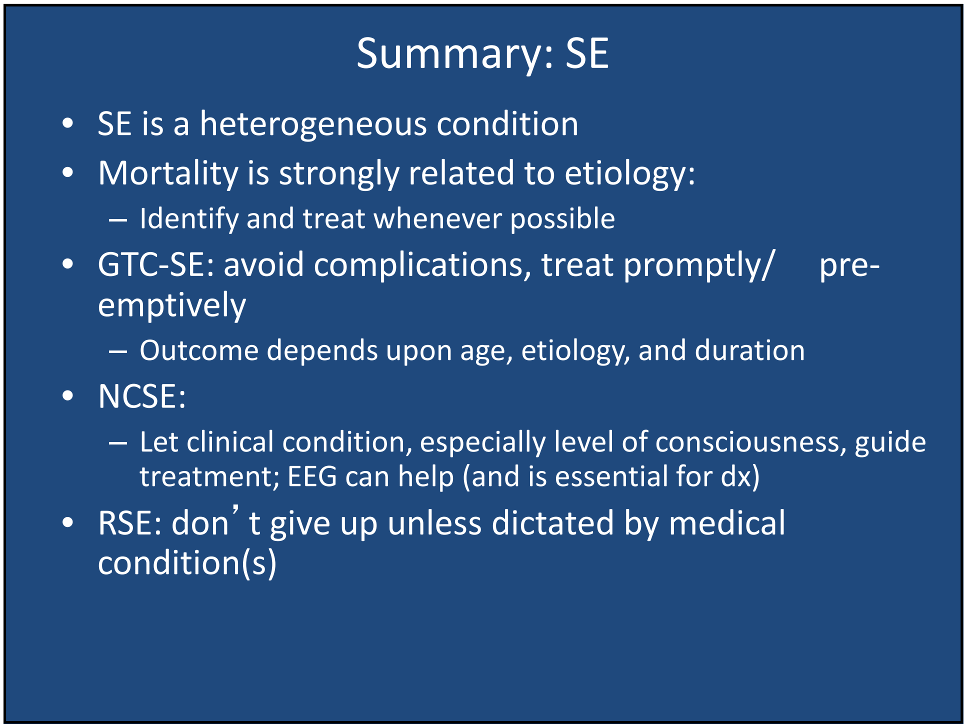
Chong & Hirsch, 2005



Summary: Seizures/Epilepsy

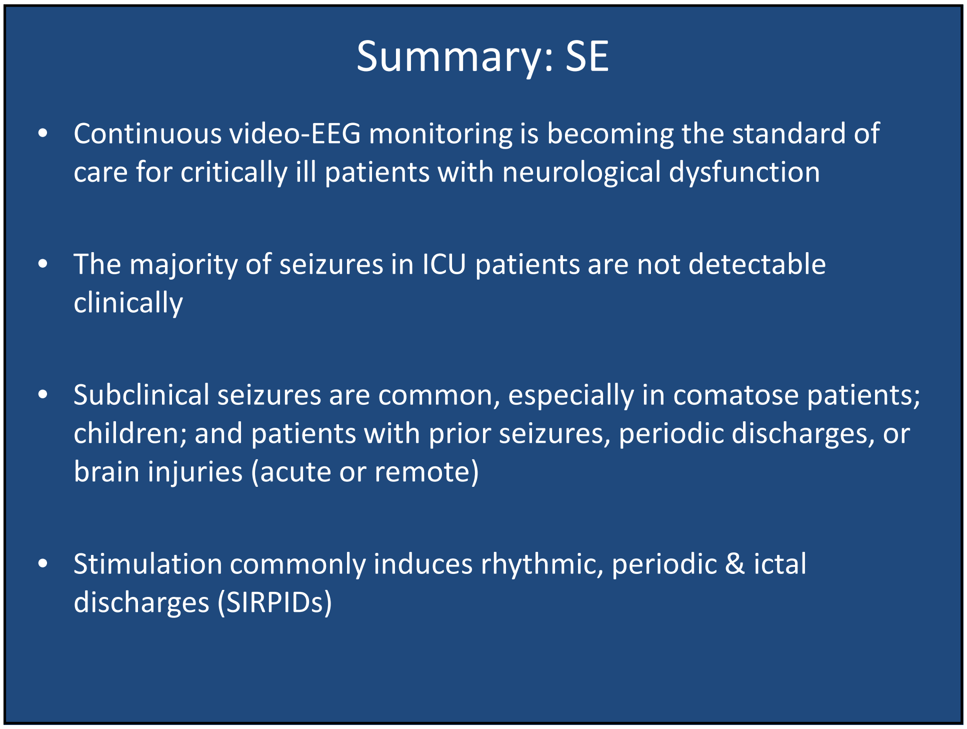
- Seizures and epilepsy have a variety of causes and potential treatments.

- Acute symptomatic seizures are common in the ICU.
  - Removal of precipitating factors is critical.
  - AEDs are used selectively.



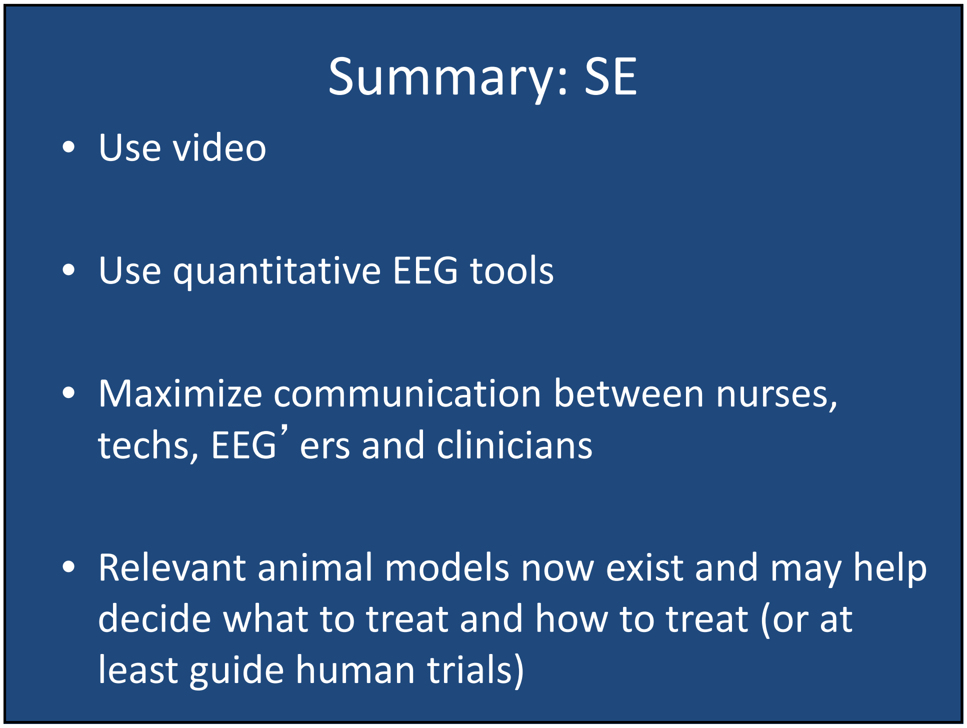
Summary: SE

- SE is a heterogeneous condition
- Mortality is strongly related to etiology:
  - Identify and treat whenever possible
- GTC-SE: avoid complications, treat promptly/ pre-emptively
  - Outcome depends upon age, etiology, and duration
- NCSE:
  - Let clinical condition, especially level of consciousness, guide treatment; EEG can help (and is essential for dx)
- RSE: don’t give up unless dictated by medical condition(s)



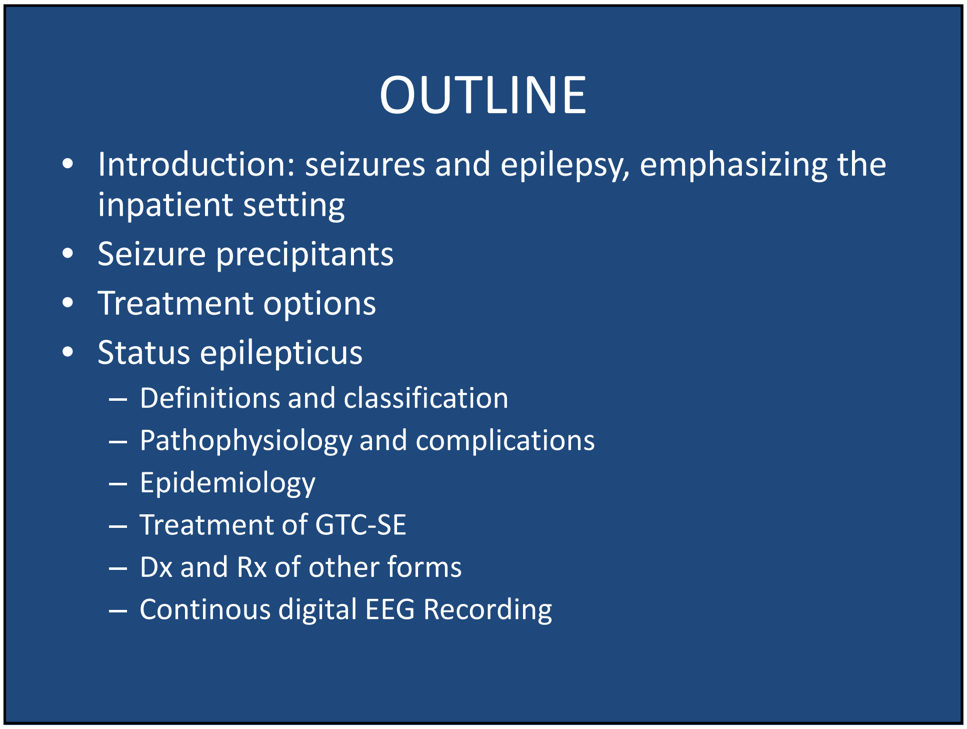
Summary: SE

- Continuous video-EEG monitoring is becoming the standard of care for critically ill patients with neurological dysfunction
- The majority of seizures in ICU patients are not detectable clinically
- Subclinical seizures are common, especially in comatose patients; children; and patients with prior seizures, periodic discharges, or brain injuries (acute or remote)
- Stimulation commonly induces rhythmic, periodic & ictal discharges (SIRPIDs)



Summary: SE

- Use video
- Use quantitative EEG tools
- Maximize communication between nurses, techs, EEG’ers and clinicians
- Relevant animal models now exist and may help decide what to treat and how to treat (or at least guide human trials)



OUTLINE

- Introduction: seizures and epilepsy, emphasizing the inpatient setting
- Seizure precipitants
- Treatment options
- Status epilepticus
  - Definitions and classification
  - Pathophysiology and complications
  - Epidemiology
  - Treatment of GTC-SE
  - Dx and Rx of other forms
  - Continous digital EEG Recording

Thank you

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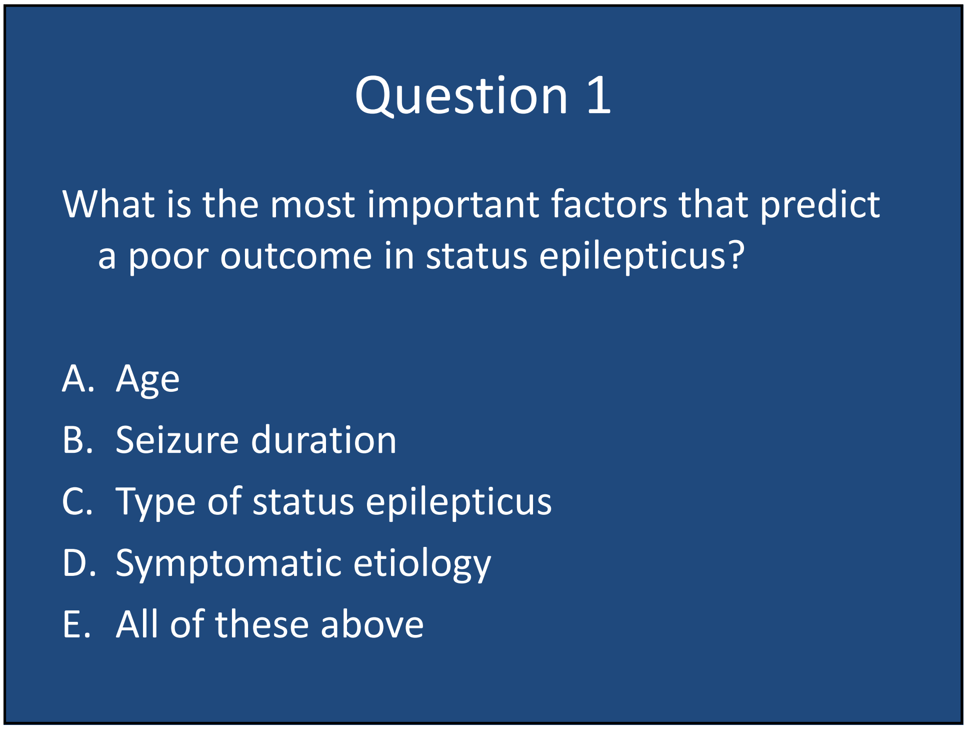
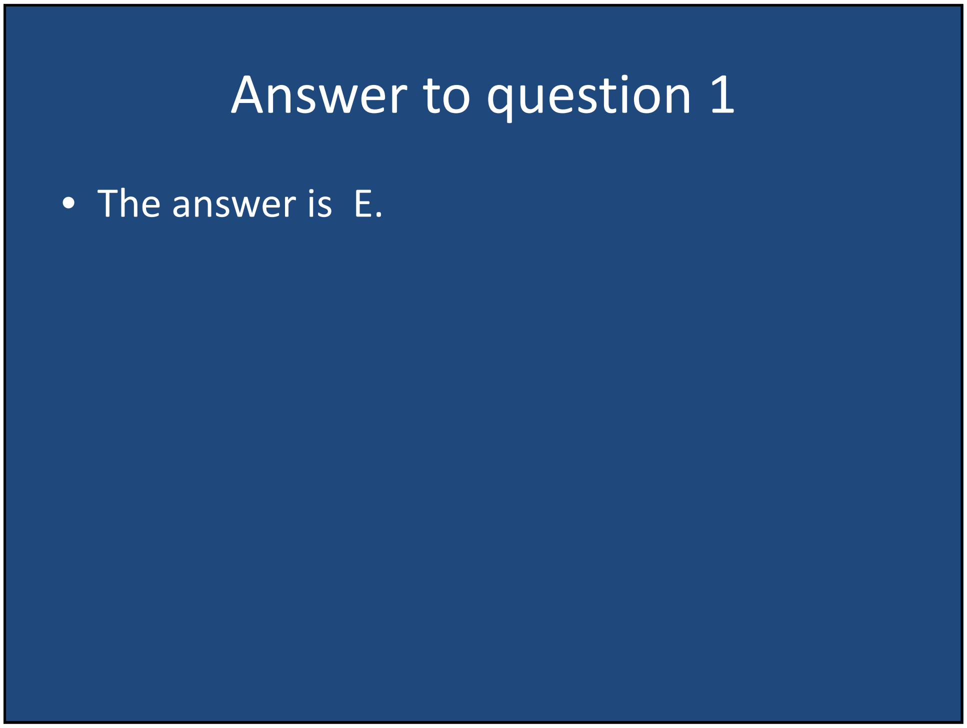


Question 1

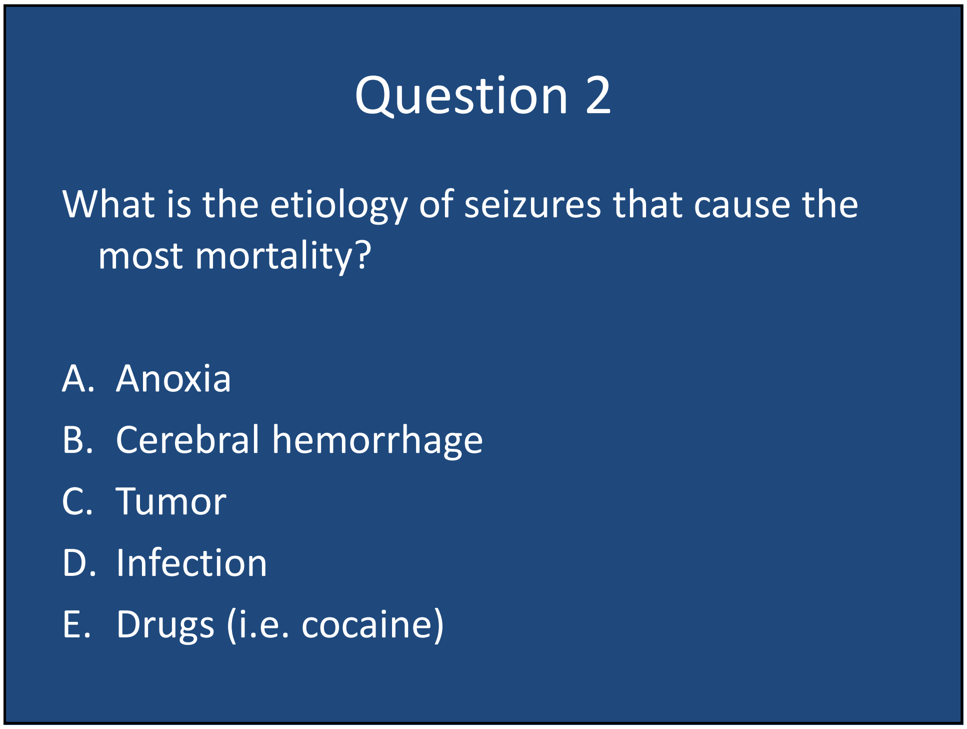
What is the most important factors that predict a poor outcome in status epilepticus?

A. Age
B. Seizure duration
C. Type of status epilepticus
D. Symptomatic etiology
E. All of these above



Answer to question 1

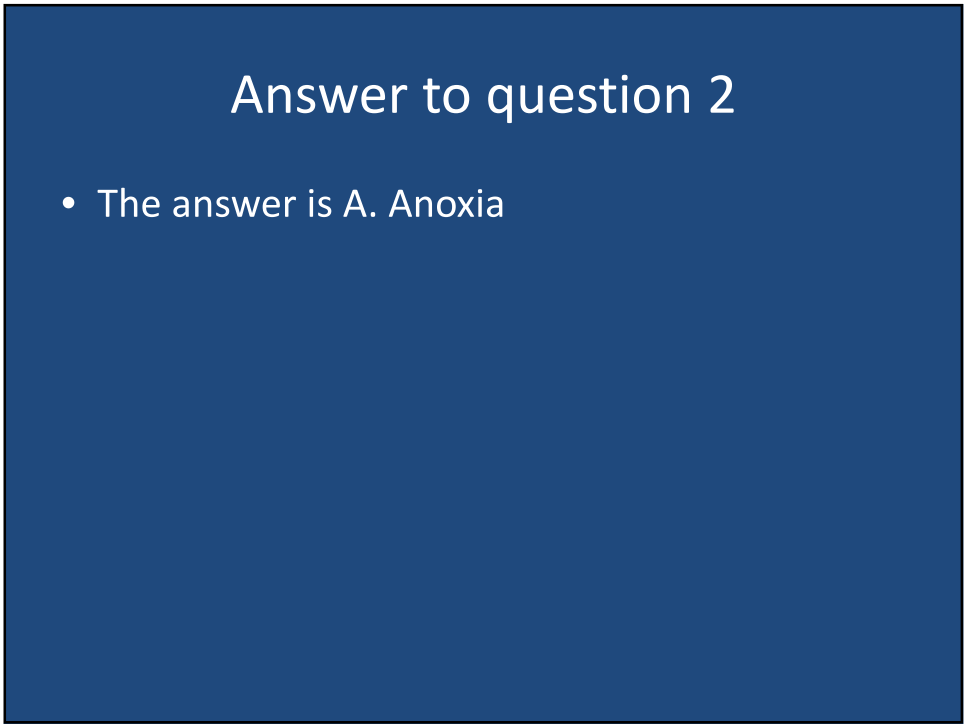
- The answer is E.



Question 2

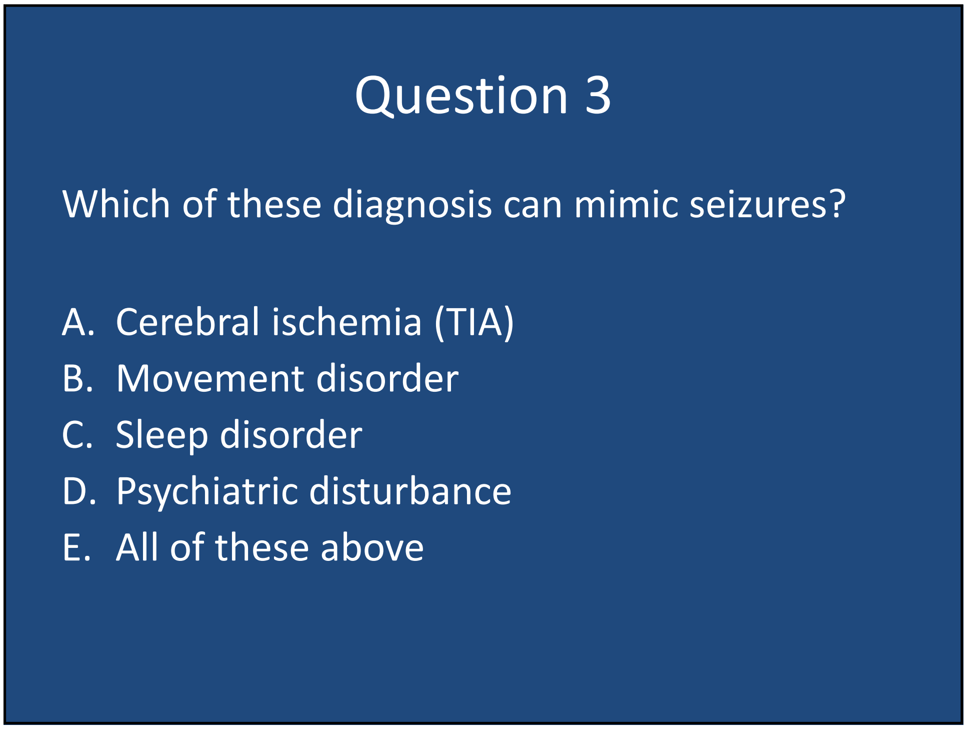
What is the etiology of seizures that cause the most mortality?

A. Anoxia
B. Cerebral hemorrhage
C. Tumor
D. Infection
E. Drugs (i.e. cocaine)



Answer to question 2

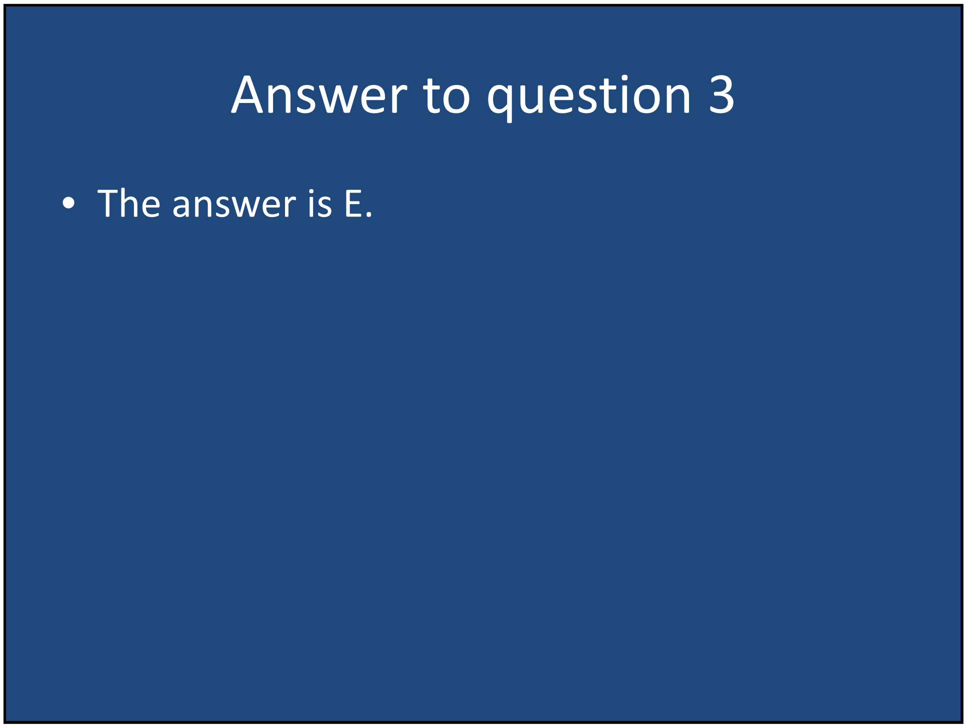
- The answer is A. Anoxia



Question 3

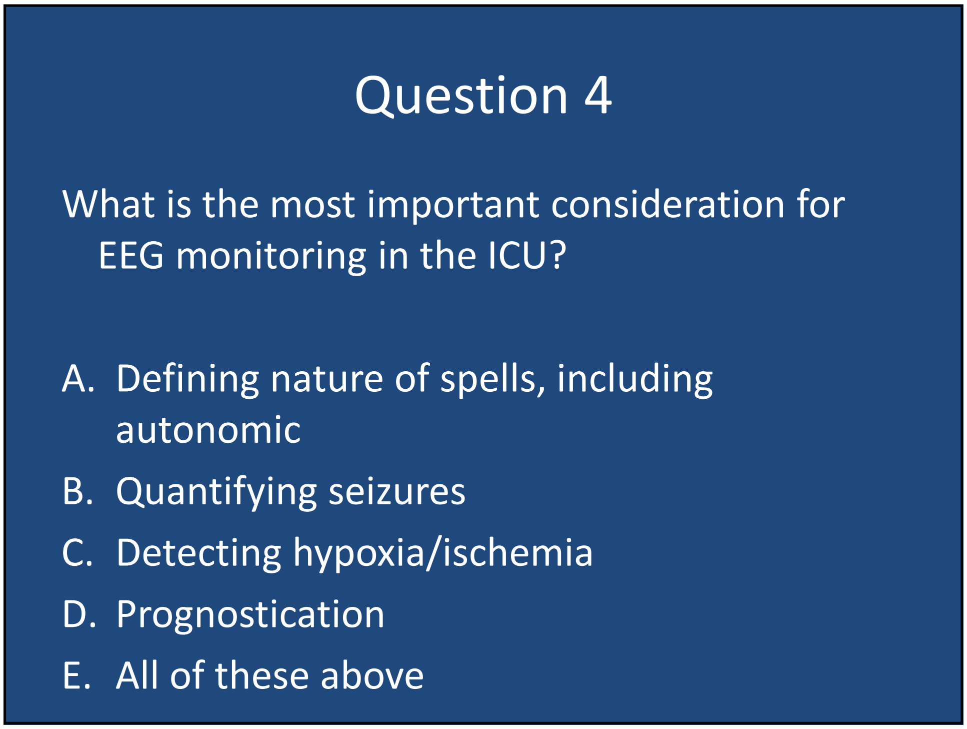
Which of these diagnosis can mimic seizures?

A. Cerebral ischemia (TIA)
B. Movement disorder
C. Sleep disorder
D. Psychiatric disturbance
E. All of these above



Answer to question 3

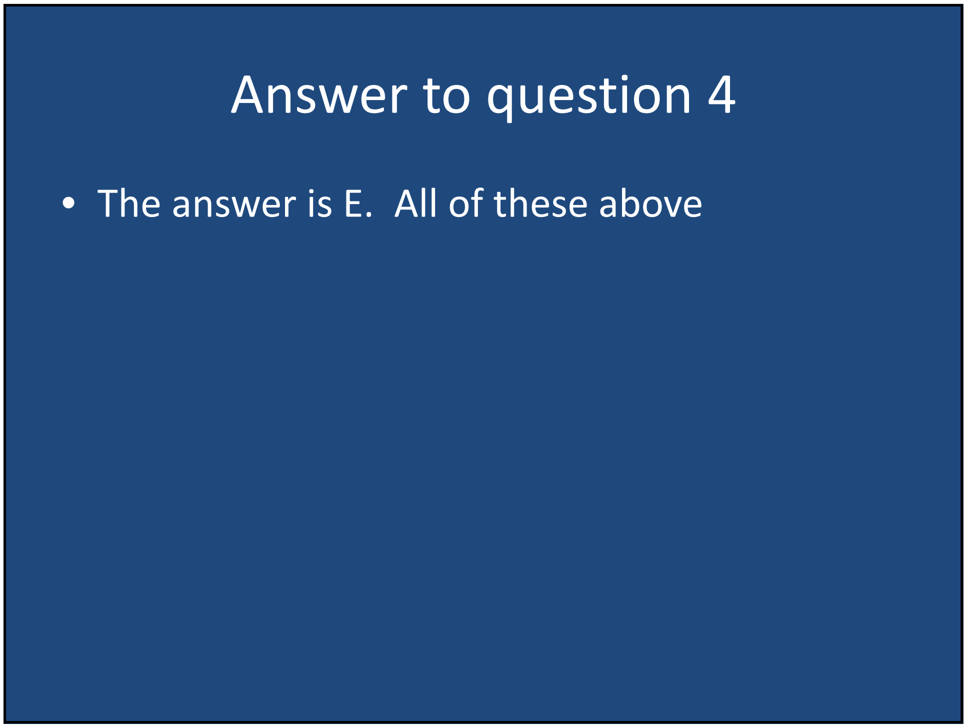
- The answer is E.



Question 4

What is the most important consideration for EEG monitoring in the ICU?

A. Defining nature of spells, including autonomic
B. Quantifying seizures
C. Detecting hypoxia/ischemia
D. Prognostication
E. All of these above



Answer to question 4

- The answer is E. All of these above

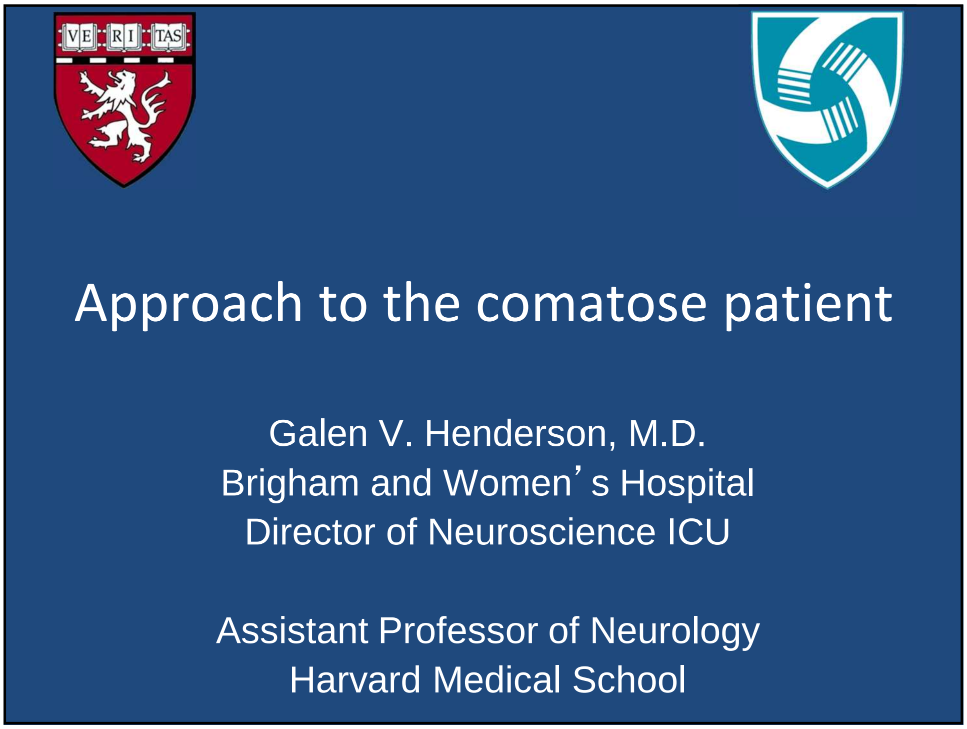
Question 5

What is the most important initial management of a seizure?

A. Airway/ventilation/O2
B. Paralytics
C. Blood: glucose, electrolytes, BUN, ABG, AED levels, toxic screen
D. IV: normal saline X 2
E. All of these above

Answer to Question 5

- The answer is A. Protection/securing of the airway.



Approach to the comatose patient

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Assistant Professor of Neurology
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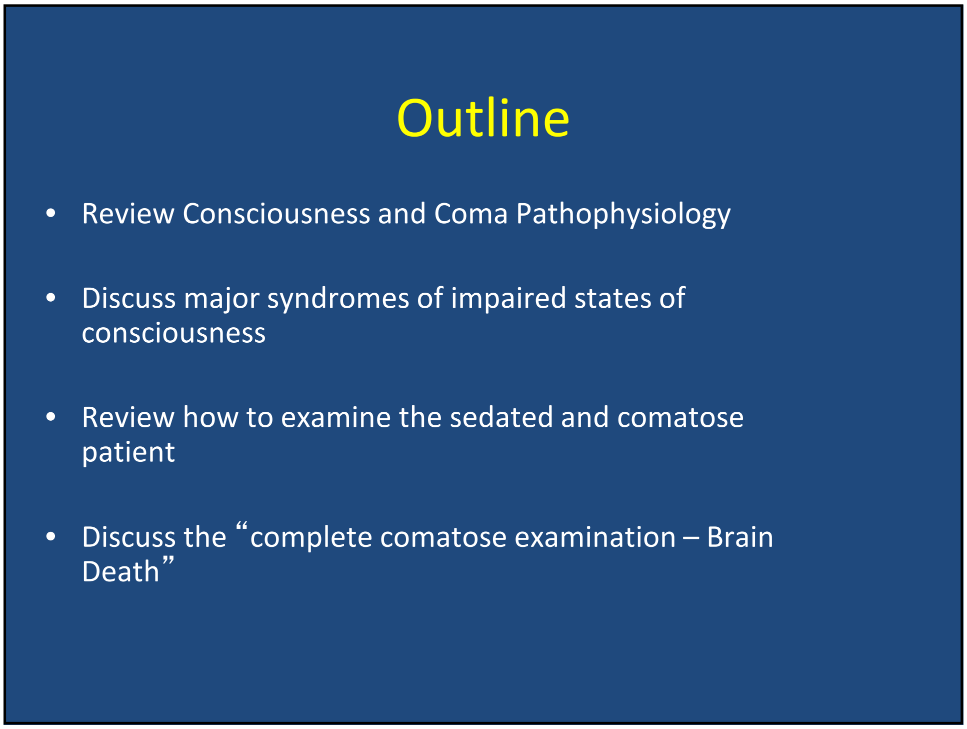
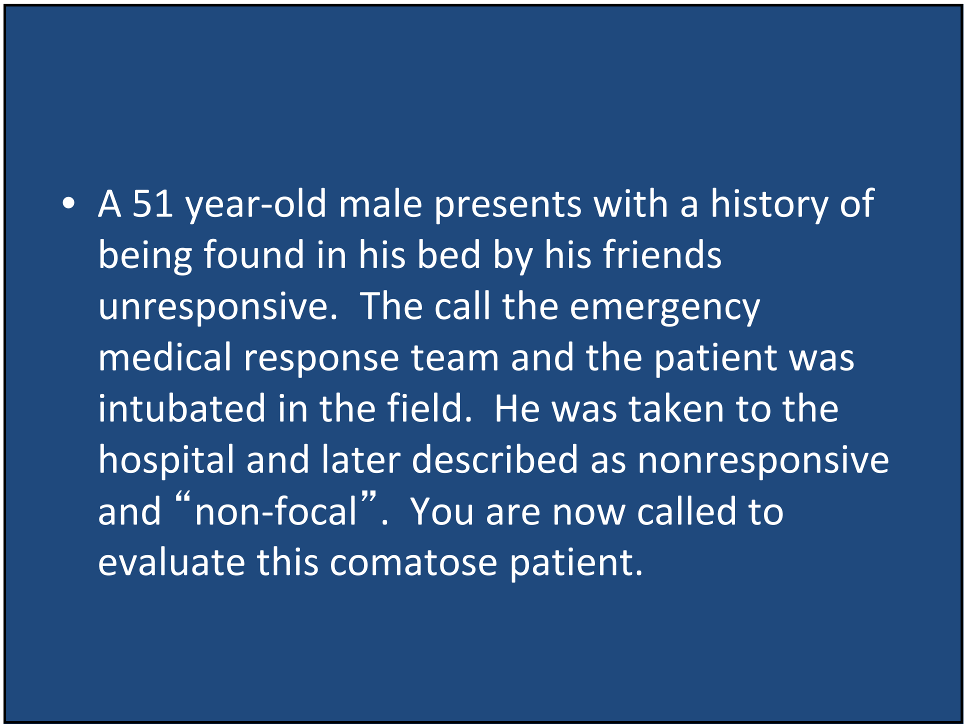
Disclosures

- I have no industry relationships



Outline

- Review Consciousness and Coma Pathophysiology
- Discuss major syndromes of impaired states of consciousness
- Review how to examine the sedated and comatose patient
- Discuss the “complete comatose examination – Brain Death”

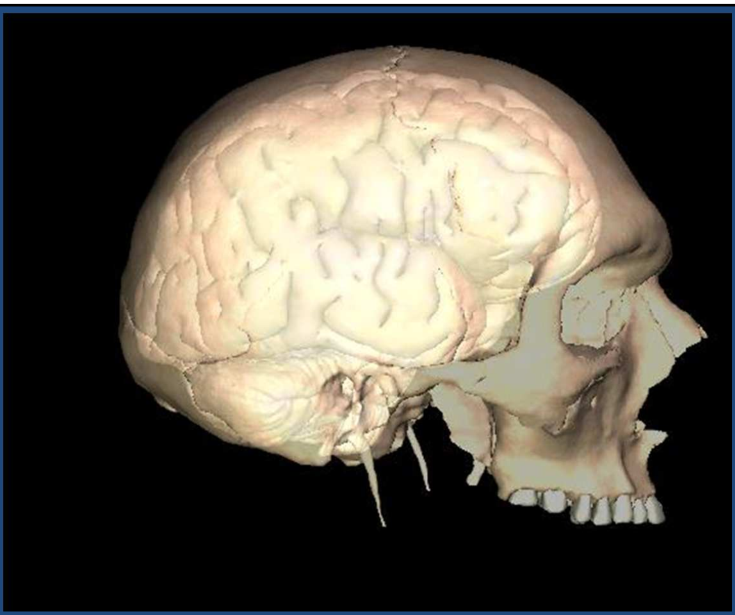


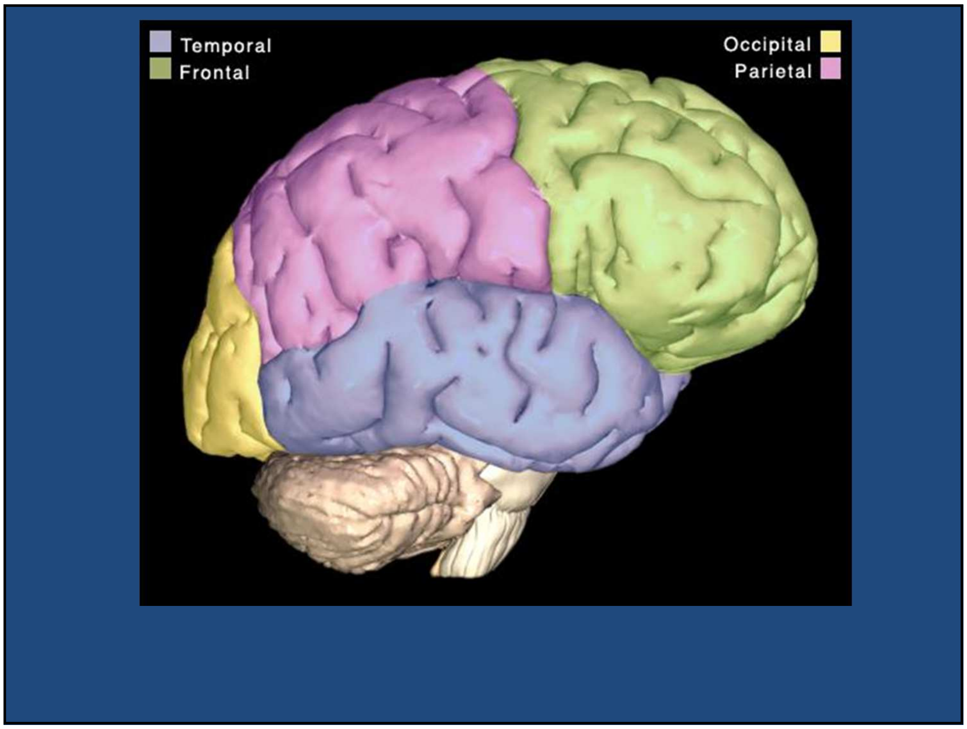
- A 51 year-old male presents with a history of being found in his bed by his friends unresponsive. The call the emergency medical response team and the patient was intubated in the field. He was taken to the hospital and later described as nonresponsive and “non-focal”. You are now called to evaluate this comatose patient.

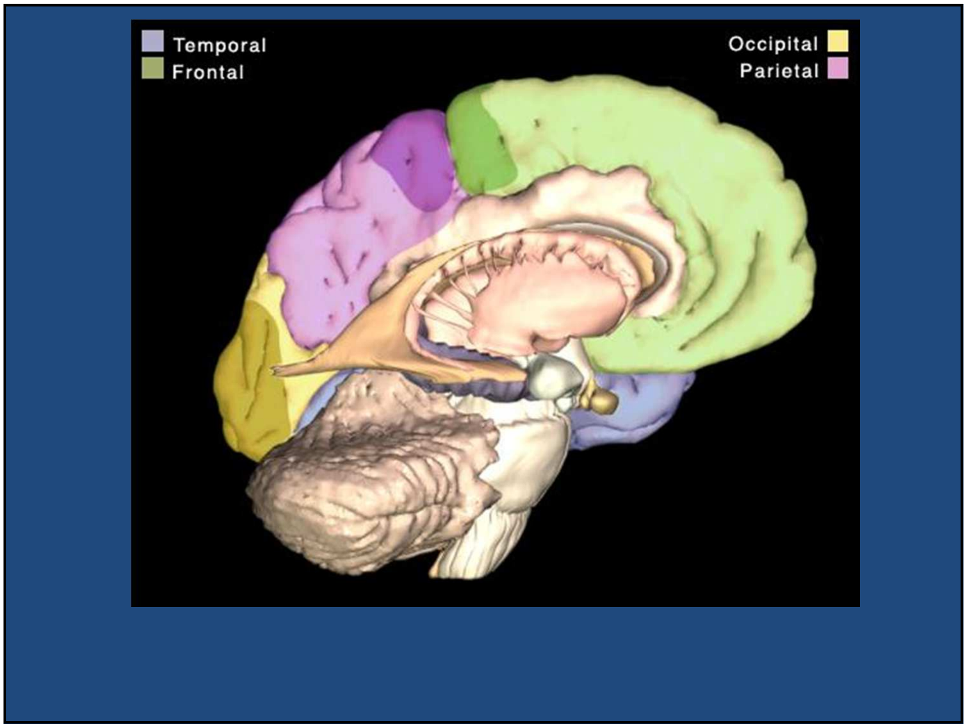
Neurological exam is important

Remains a critical way station in the clinical decision-making process.

- Does the patient who just collapsed on the street have cardiac disease or an cerebral hemorrhage?
- Is the patient with back pain, leg weakness and numbness suffering from degenerative joint disease or from impending spinal cord compression?
- Does the patient with nausea and vomiting need a gastroenterology consult or a head CT to evaluate for a brain tumor and increased intracranial pressure?




Temporal
Frontal
Occipital
Parietal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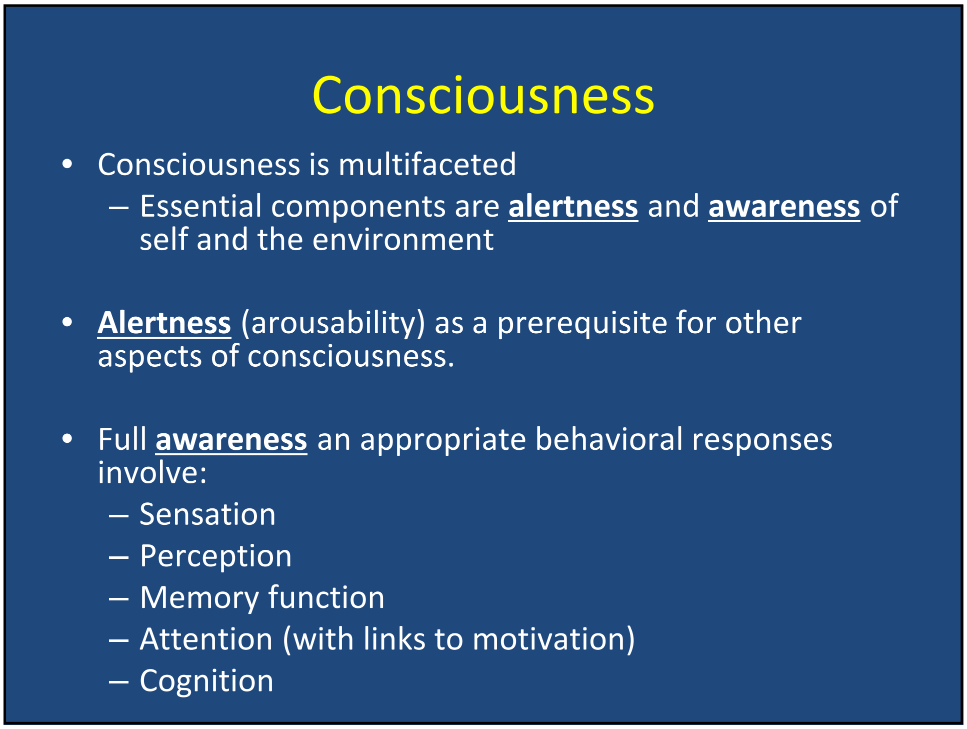
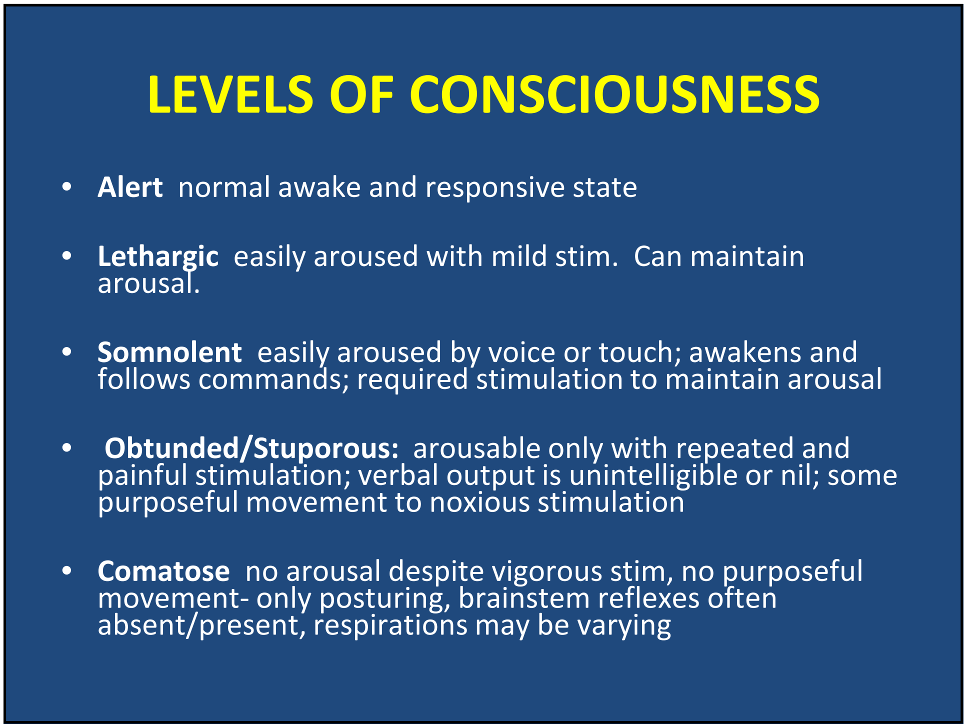


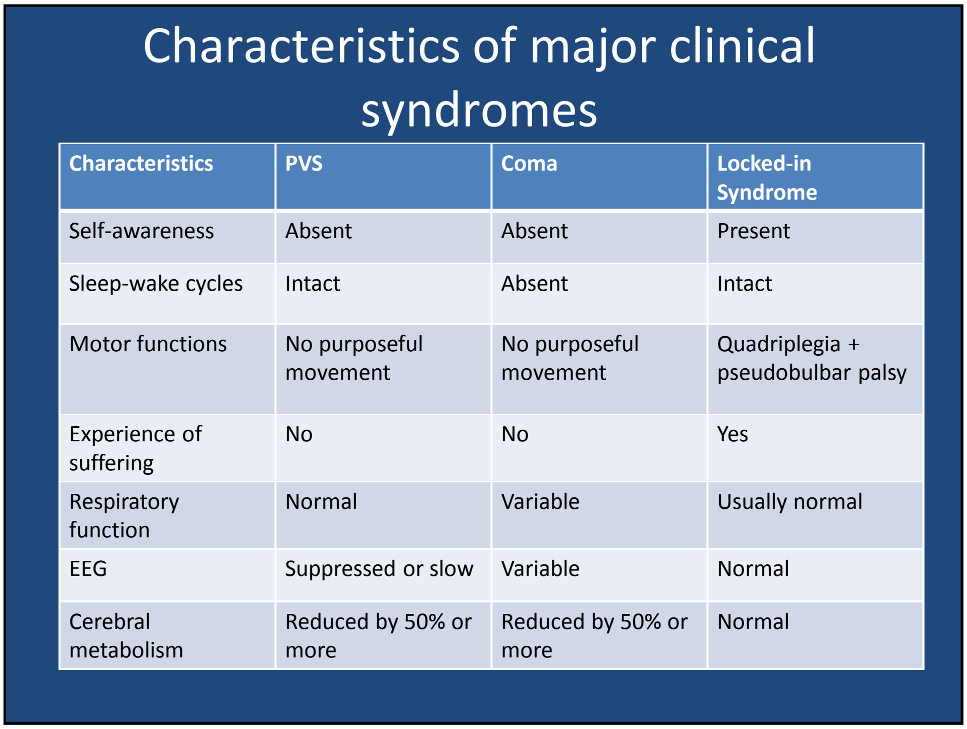
Consciousness

- Consciousness is multifaceted
  - Essential components are **alertness** and **awareness** of self and the environment
- **Alertness** (arousability) as a prerequisite for other aspects of consciousness.
- Full **awareness** an appropriate behavioral responses involve:
  - Sensation
  - Perception
  - Memory function
  - Attention (with links to motivation)
  - Cognition



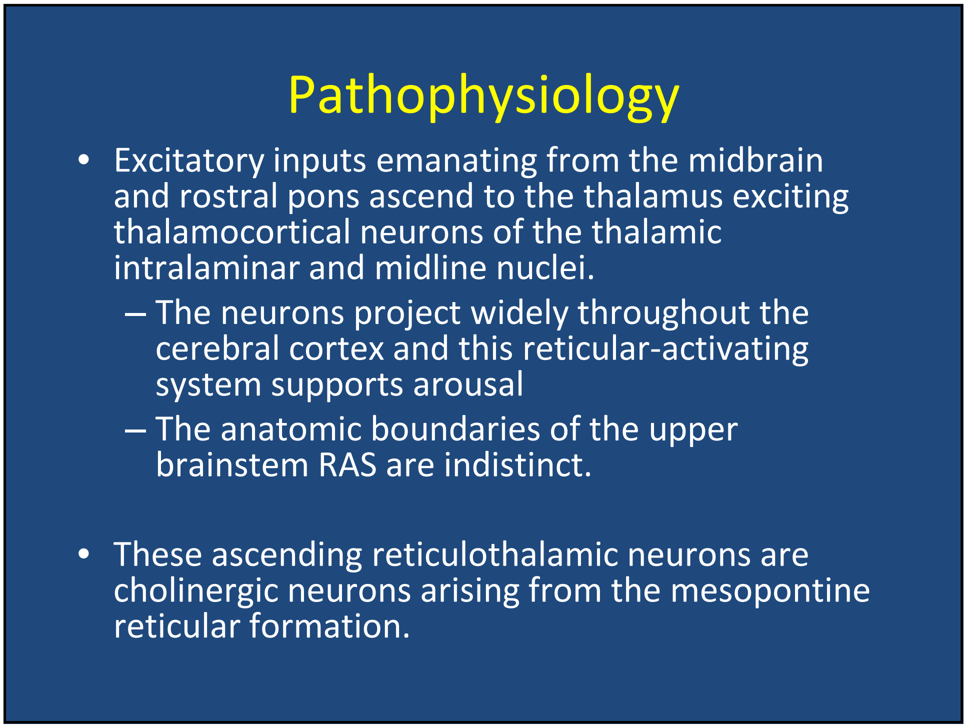
LEVELS OF CONSCIOUSNESS

- **Alert** normal awake and responsive state
- **Lethargic** easily aroused with mild stim. Can maintain arousal.
- **Somnolent** easily aroused by voice or touch; awakens and follows commands; required stimulation to maintain arousal
- **Obtunded/Stuporous:** arousable only with repeated and painful stimulation; verbal output is unintelligible or nil; some purposeful movement to noxious stimulation
- **Comatose** no arousal despite vigorous stim, no purposeful movement- only posturing, brainstem reflexes often absent/present, respirations may be varying



Characteristics of major clinical syndromes

Characteristics	**PVS**	**Coma**	**Locked-in Syndrome**
Self-awareness	Absent	Absent	Present
Sleep-wake cycles	Intact	Absent	Intact
Motor functions	No purposeful movement	No purposeful movement	Quadriplegia + pseudobulbar palsy
Experience of suffering	No	No	Yes
Respiratory function	Normal	Variable	Usually normal
EEG	Suppressed or slow	Variable	Normal
Cerebral metabolism	Reduced by 50% or more	Reduced by 50% or more	Normal

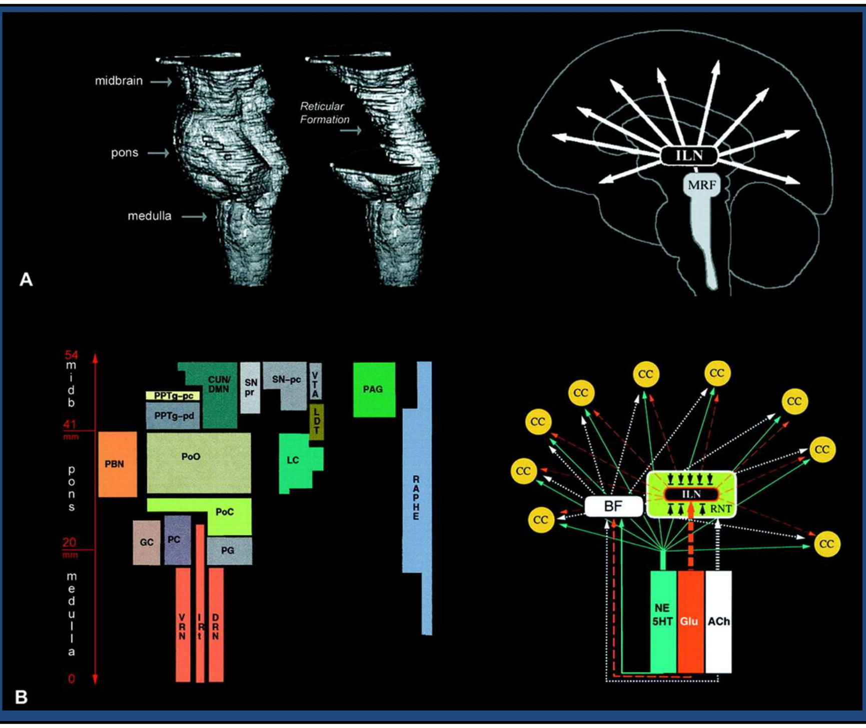


Pathophysiology

- Excitatory inputs emanating from the midbrain and rostral pons ascend to the thalamus exciting thalamocortical neurons of the thalamic intralaminar and midline nuclei.
  - The neurons project widely throughout the cerebral cortex and this reticular-activating system supports arousal
  - The anatomic boundaries of the upper brainstem RAS are indistinct.
- These ascending reticulothalamic neurons are cholinergic neurons arising from the mesopontine reticular formation.

Pathophysiology

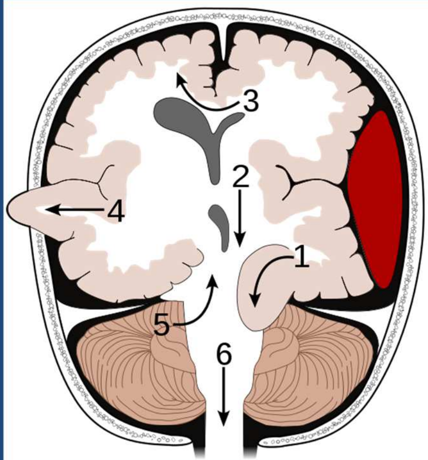
- Attention is thought to depend on the diffuse arousal system and cortical systems for directed attention in various spheres:
  - Posterior parietal lobes (sensory awareness).
  - The frontal association cortex (motor attention: directed movements of the eyes, limbs, and body).
  - Cingulated cortex (motivational aspects of attention).


midbrain
pons
medulla
Reticular Formation
A
ILN
MRF
54
midb
41 mm
pons
20 mm
medulla
0
CUN/ DMN
SN pr
SN-pc
VTA
PPTg-pc
PPTg-pd
LDT
PAG
PBN
PoO
LC
RAPHE
PoC
GC
PC
PG
VRN
IRt
DRN
B
CC
BF
ILN
RNT
NE 5HT
Glu
ACh

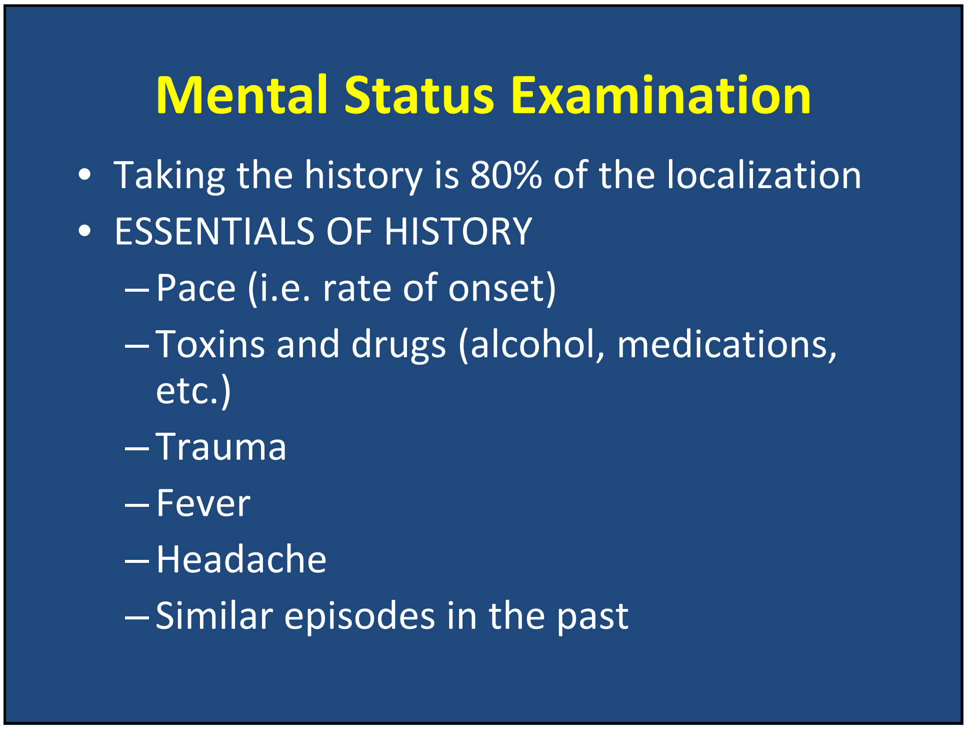
PATHOPHYSIOLOGY OF COMA

- Bilateral diffuse hemisphere disease
- Brainstem reticular formation disease

Cerebral Herniation Syndromes

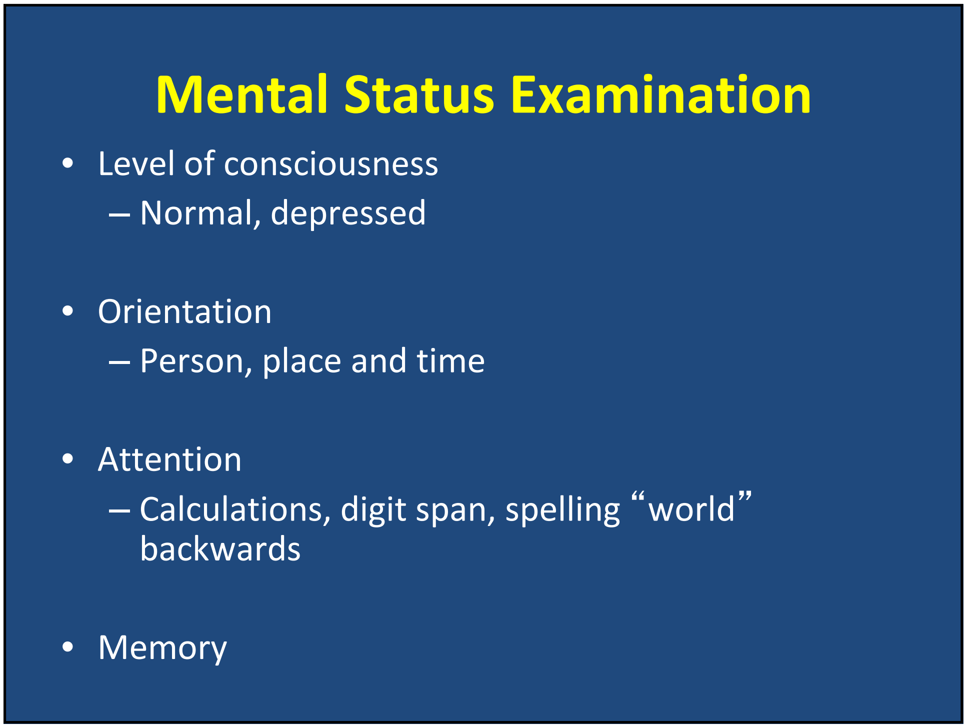


- Decreased cerebral perfusion pressure causing ischemia
- Midline shift causing ventricular obstruction
- Types
  1. Uncal
  2. Central (and # 6)
  3. Cingulate (subfalcine)
  4. Transcalvarial
  5. Cerebellar



Mental Status Examination

- Taking the history is 80% of the localization
- ESSENTIALS OF HISTORY
  - Pace (i.e. rate of onset)
  - Toxins and drugs (alcohol, medications, etc.)
  - Trauma
  - Fever
  - Headache
  - Similar episodes in the past



Mental Status Examination

- Level of consciousness
  - Normal, depressed
- Orientation
  - Person, place and time
- Attention
  - Calculations, digit span, spelling “world” backwards
- Memory

The Examination

- Watching the patient for yields considerable information
  - The predominant postures of the limbs and body; the presence or absence of spontaneous movements one side; the position of the head and eyes; and the rate, depth, and rhythm of respirations give substantial formation

- Level of consciousness is then noted by the patients reaction to:
  - Calling of his/her name
  - Simple commands
  - Noxious stimuli such as tickling the nares, supraorbital or sternal pressure, pinching the side of the neck or inner parts of the arms or thighs, or applying pressure to the nail beds

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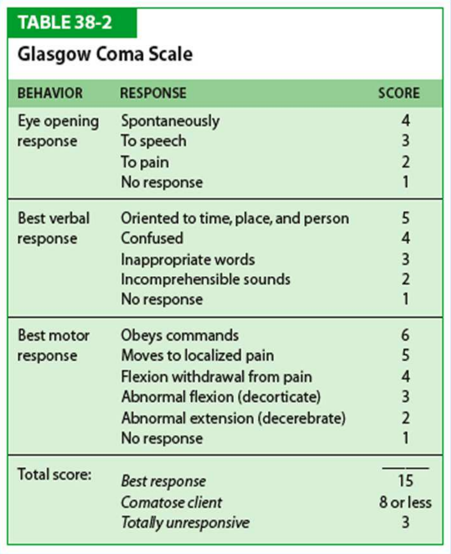
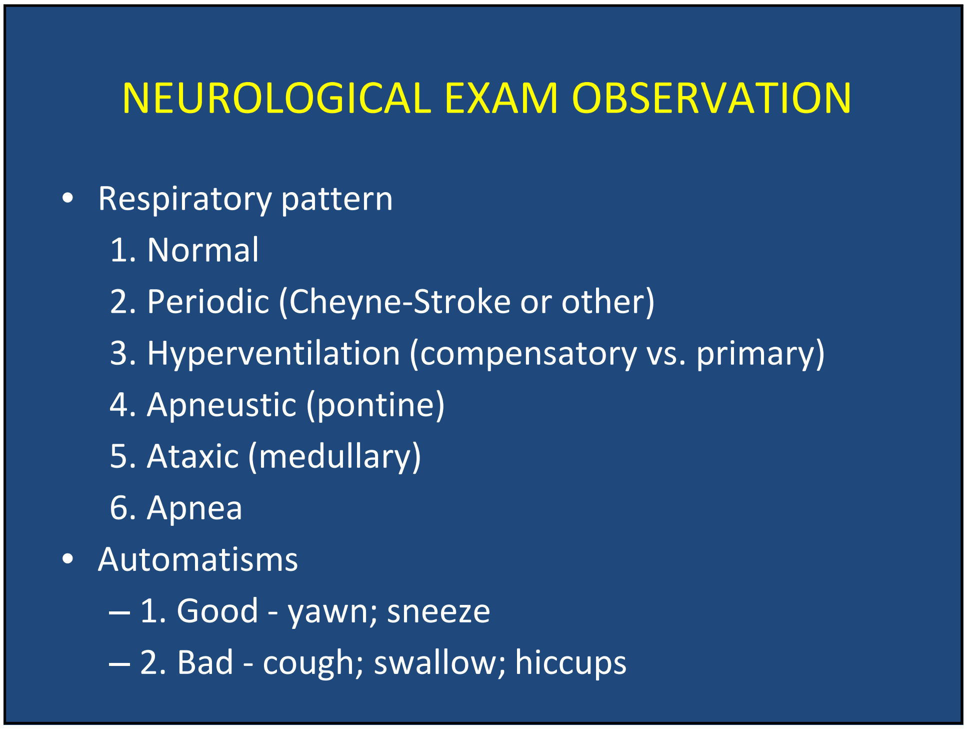


TABLE 38-2

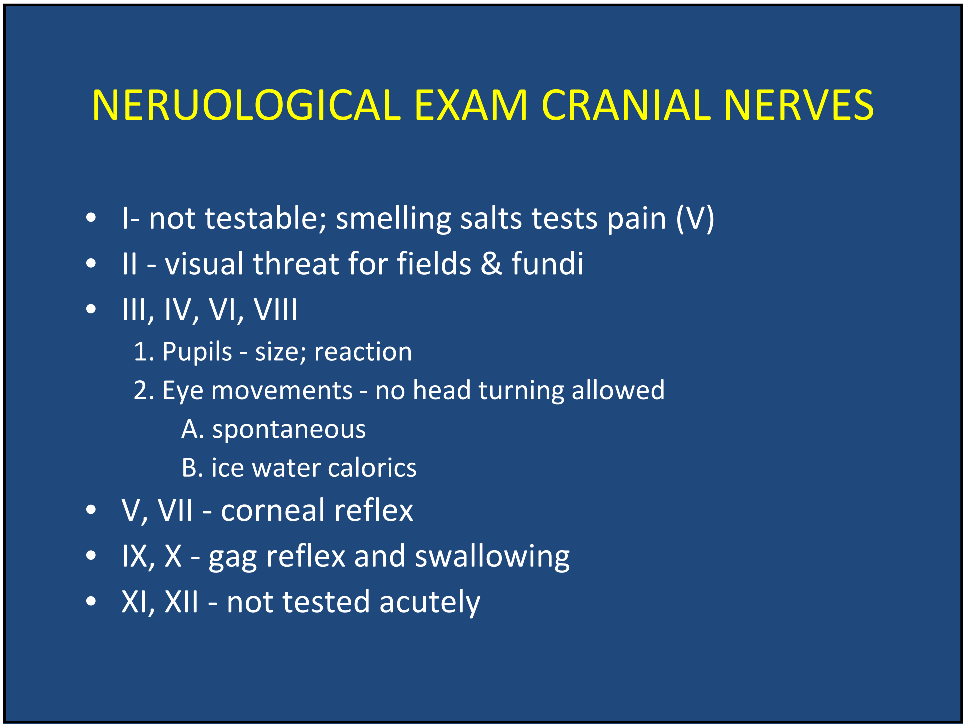
Glasgow Coma Scale

BEHAVIOR	RESPONSE	SCORE
Eye opening response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented to time, place, and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1
Total score:	*Best response*	15
	Comatose client	8 or less
	Totally unresponsive	3



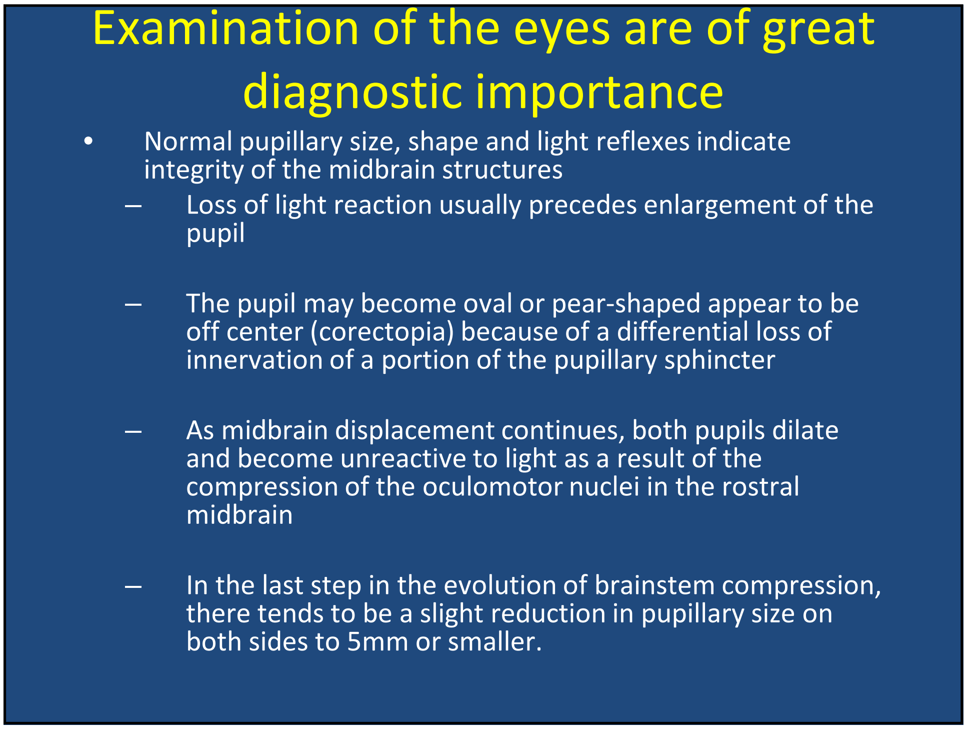
NEUROLOGICAL EXAM OBSERVATION

- Respiratory pattern
  1. Normal
  2. Periodic (Cheyne-Stroke or other)
  3. Hyperventilation (compensatory vs. primary)
  4. Apneustic (pontine)
  5. Ataxic (medullary)
  6. Apnea
- Automatisms
  - 1. Good - yawn; sneeze
  - 2. Bad - cough; swallow; hiccups



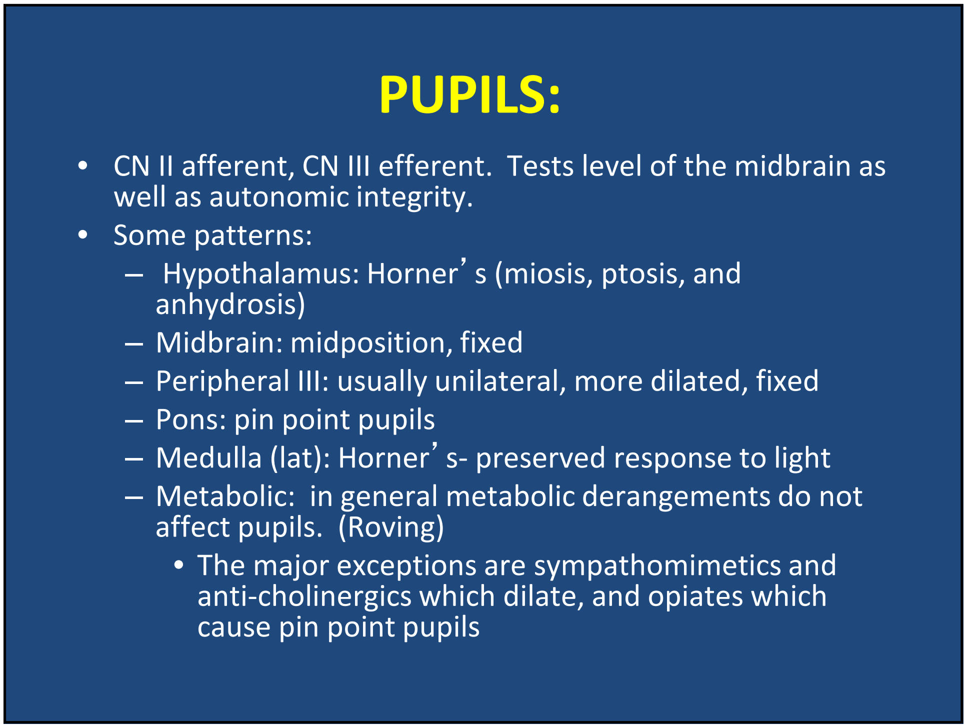
NERUOLOGICAL EXAM CRANIAL NERVES

- I- not testable; smelling salts tests pain (V)
- II - visual threat for fields & fundi
- III, IV, VI, VIII
  1. Pupils - size; reaction
  2. Eye movements - no head turning allowed
     A. spontaneous
     B. ice water calorics
- V, VII - corneal reflex
- IX, X - gag reflex and swallowing
- XI, XII - not tested acutely



Examination of the eyes are of great diagnostic importance

- Normal pupillary size, shape and light reflexes indicate integrity of the midbrain structures
  - Loss of light reaction usually precedes enlargement of the pupil
  - The pupil may become oval or pear-shaped appear to be off center (corectopia) because of a differential loss of innervation of a portion of the pupillary sphincter
  - As midbrain displacement continues, both pupils dilate and become unreactive to light as a result of the compression of the oculomotor nuclei in the rostral midbrain
  - In the last step in the evolution of brainstem compression, there tends to be a slight reduction in pupillary size on both sides to 5mm or smaller.



PUPILS:

- CN II afferent, CN III efferent. Tests level of the midbrain as well as autonomic integrity.
- Some patterns:
  - Hypothalamus: Horner's (miosis, ptosis, and anhydrosis)
  - Midbrain: midposition, fixed
  - Peripheral III: usually unilateral, more dilated, fixed
  - Pons: pin point pupils
  - Medulla (lat): Horner's- preserved response to light
  - Metabolic: in general metabolic derangements do not affect pupils. (Roving)
    - The major exceptions are sympathomimetics and anti-cholinergics which dilate, and opiates which cause pin point pupils

Vertical Eye Movements

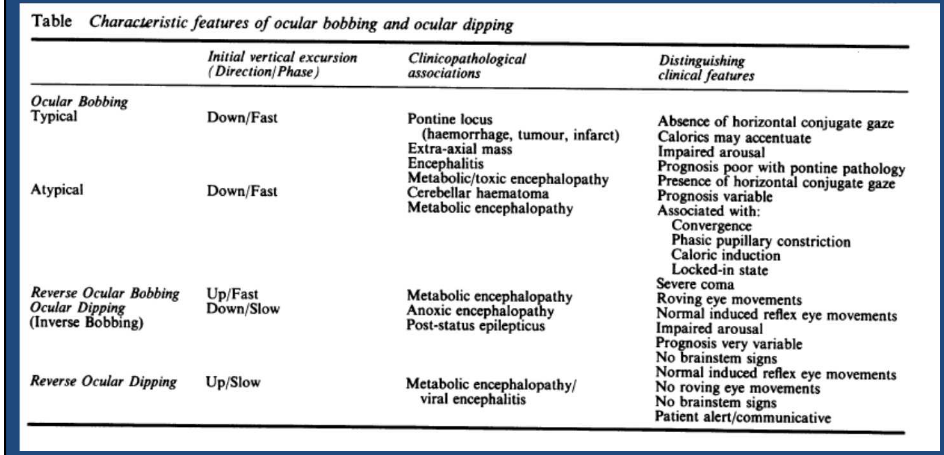


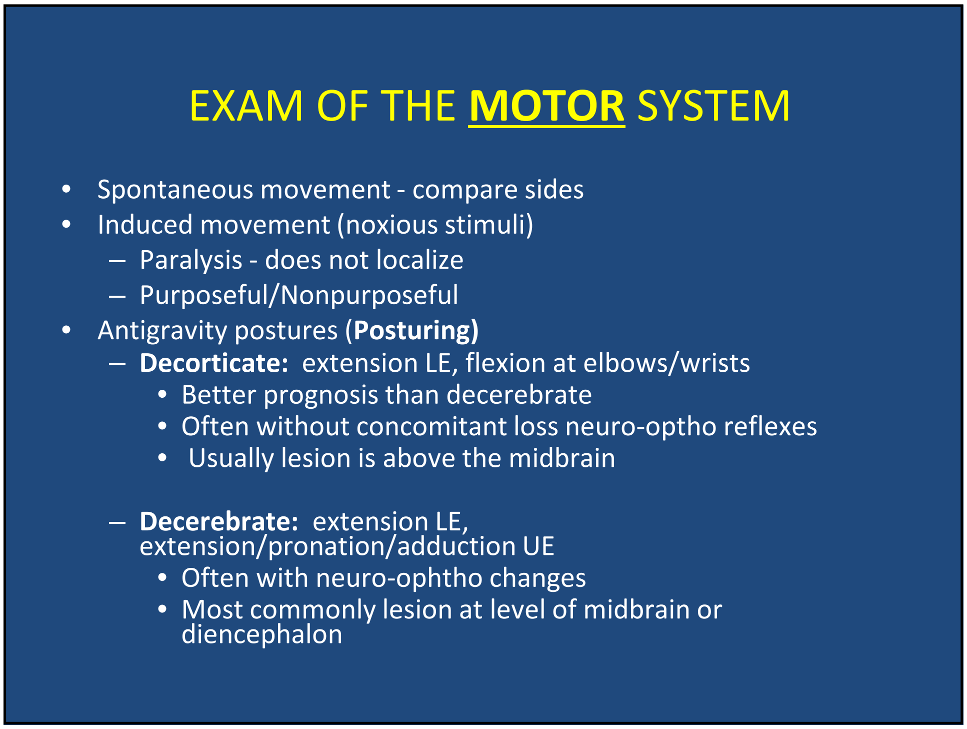
Table *Characteristic features of ocular bobbing and ocular dipping*

	Initial vertical excursion (Direction/Phase)	*Clinicopathological associations*	*Distinguishing clinical features*
Ocular Bobbing			
Typical	Down/Fast	Pontine locus (haemorrhage, tumour, infarct) Extra-axial mass Encephalitis	Absence of horizontal conjugate gaze Calorics may accentuate Impaired arousal Prognosis poor with pontine pathology
Atypical	Down/Fast	Metabolic/toxic encephalopathy Cerebellar haematoma Metabolic encephalopathy	Presence of horizontal conjugate gaze Prognosis variable Associated with: Convergence Phasic pupillary constriction Caloric induction Locked-in state
Reverse Ocular Bobbing *Ocular Dipping* (Inverse Bobbing)	Up/Fast Down/Slow	Metabolic encephalopathy Anoxic encephalopathy Post-status epilepticus	Severe coma Roving eye movements Normal induced reflex eye movements Impaired arousal Prognosis very variable No brainstem signs
Reverse Ocular Dipping	Up/Slow	Metabolic encephalopathy/ viral encephalitis	Normal induced reflex eye movements No roving eye movements No brainstem signs Patient alert/communicative

Journal of Neurology, Neurosurgery, and Psychiatry 1988;**51**:725–727

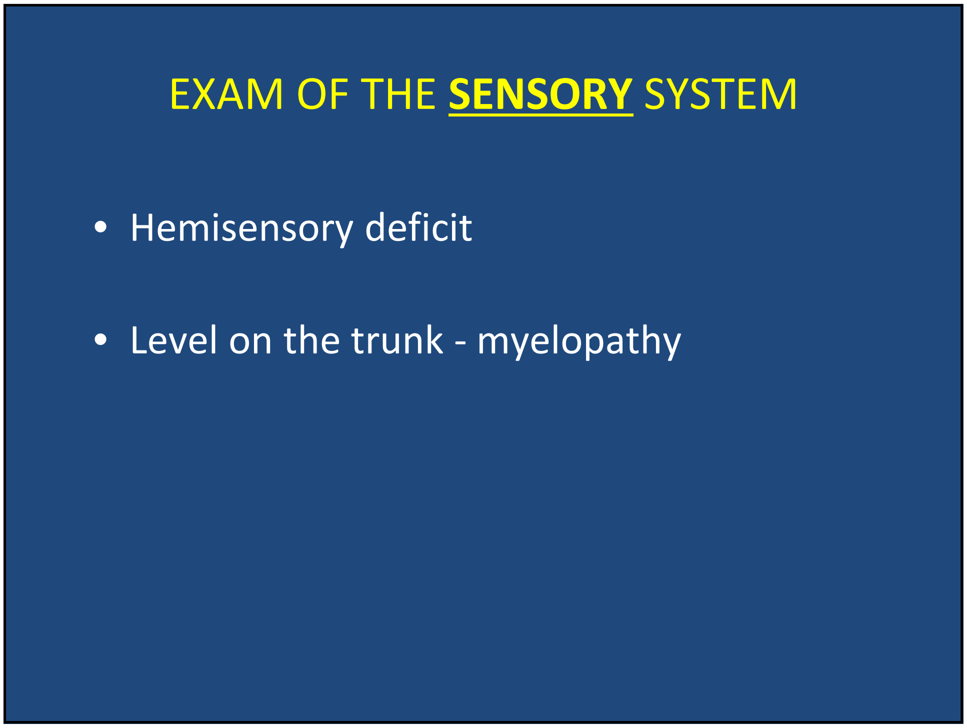
EXAM OF **CRANIAL NERVES**

- I- not testable; smelling salts tests pain (V)
- II - visual threat for fields & acuity; fundi
- III, IV, VI, VIII
  1. Pupils - size; reaction (No PERRLA)
  2. Eye movements - no head turning allowed
     A. spontaneous
     B. ice water calorics
- V, VII - corneal reflex
- IX, X - gag reflex and swallowing
- XI, XII - not tested acutely



EXAM OF THE **MOTOR** SYSTEM

- Spontaneous movement - compare sides
- Induced movement (noxious stimuli)
  - Paralysis - does not localize
  - Purposeful/Nonpurposeful
- Antigravity postures (**Posturing)**
  - **Decorticate:** extension LE, flexion at elbows/wrists
    - Better prognosis than decerebrate
    - Often without concomitant loss neuro-optho reflexes
    - Usually lesion is above the midbrain
  - **Decerebrate:** extension LE, extension/pronation/adduction UE
    - Often with neuro-ophtho changes
    - Most commonly lesion at level of midbrain or diencephalon



EXAM OF THE **SENSORY** SYSTEM

- Hemisensory deficit
- Level on the trunk - myelopathy

NEUROLOGICAL EXAM REFLEXES

- Proprioceptive (tendon jerks)
- Nocioceptive (plantar; corneal)
- Antigravity (decerebration; decortication)

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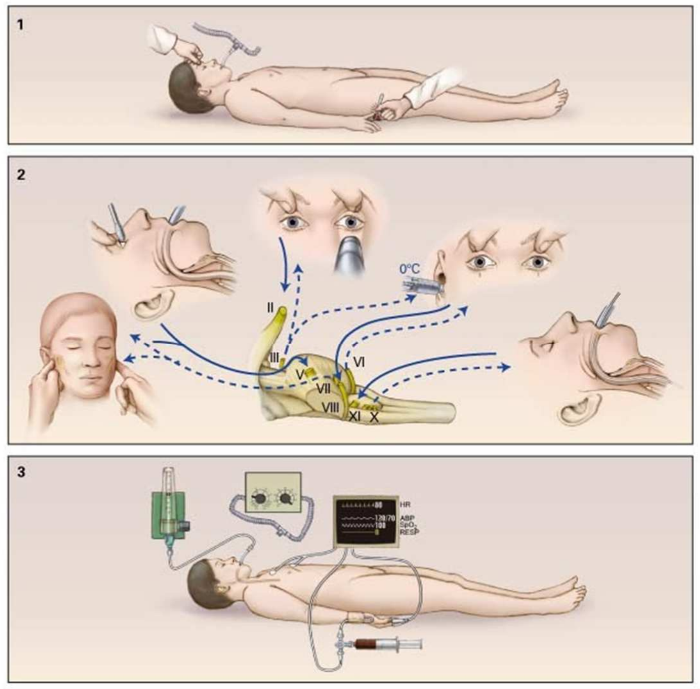
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N Engl J Med
344:1215,
April 19, 2001

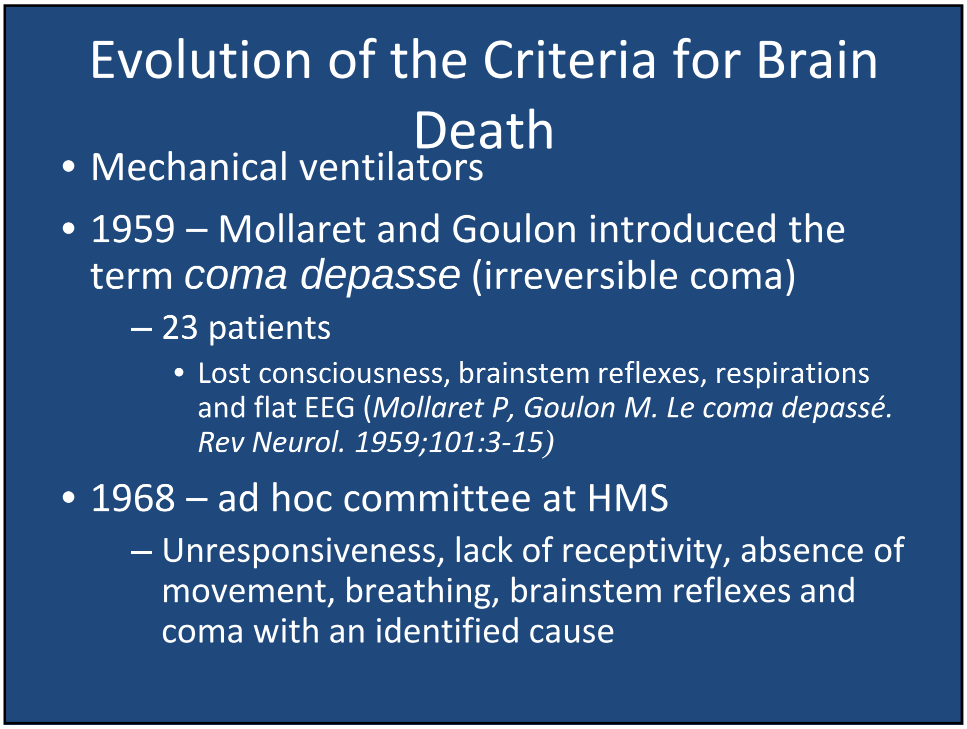
The diagnosis of death

Cardiac death
(heart stops)

- Absence of radial, carotid or femoral pulses
- Absence of heart tones at apex of heart by auscultation
- Absence of breath sounds by auscultation
- Pupils nonreactive
- Ascertain that the patient does not rouse to verbal or tactile stimuli

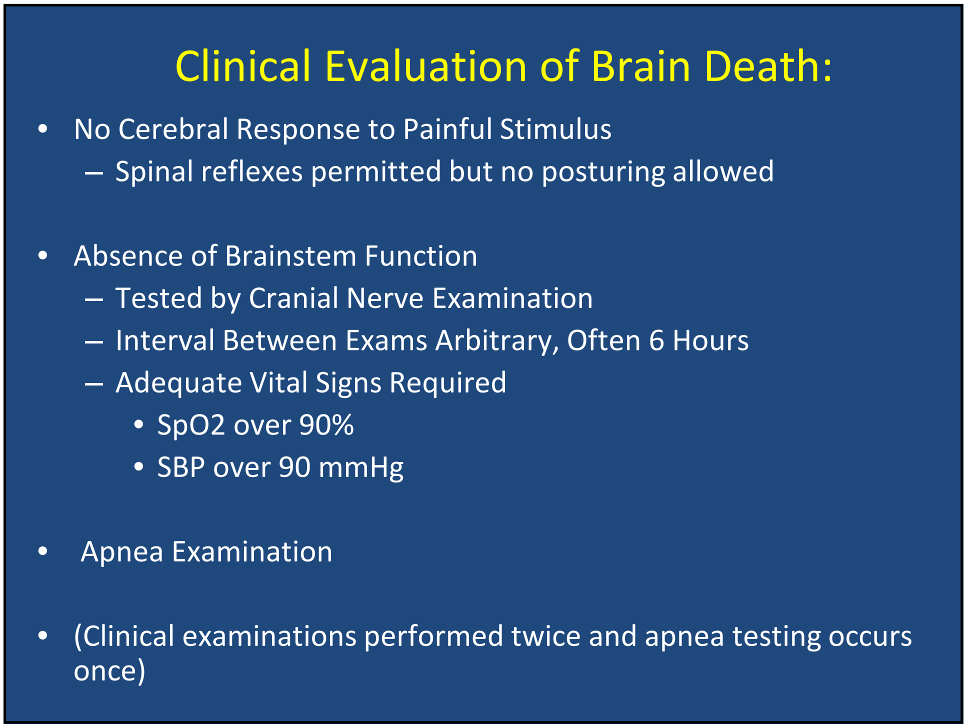
Brain death
(brain stops)

- Irreversible loss of function of the brain, including the brainstem
- Exam is much more complicated



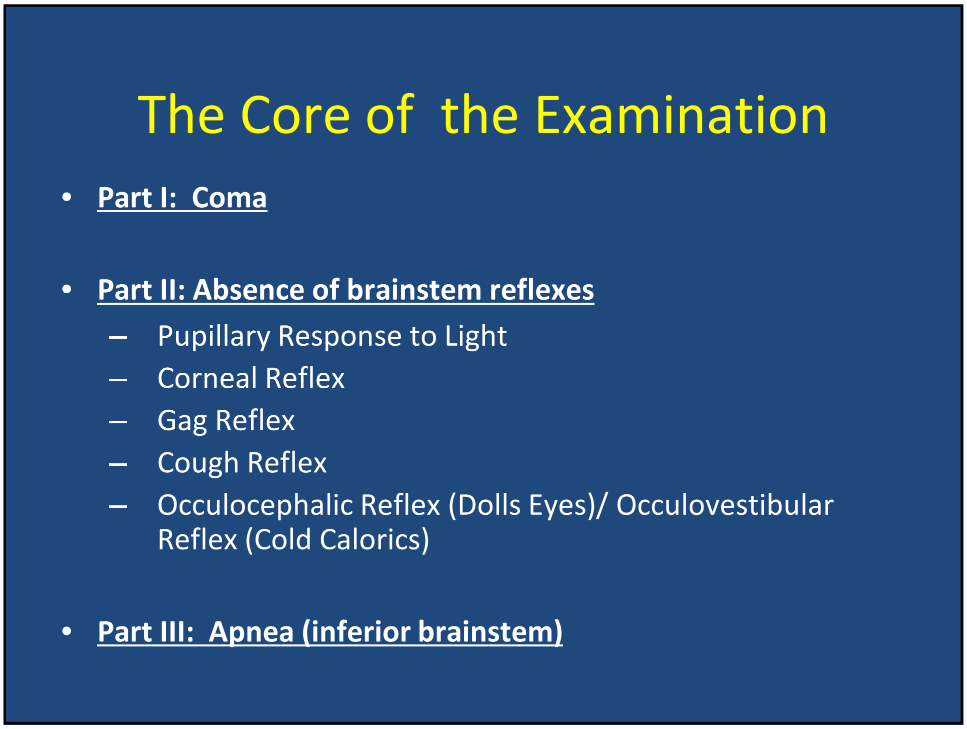
Evolution of the Criteria for Brain Death

- Mechanical ventilators
- 1959 – Mollaret and Goulon introduced the term *coma depasse* (irreversible coma)
  - 23 patients
    - Lost consciousness, brainstem reflexes, respirations and flat EEG (*Mollaret P, Goulon M. Le coma depassé. Rev Neurol. 1959;101:3-15)*
- 1968 – ad hoc committee at HMS
  - Unresponsiveness, lack of receptivity, absence of movement, breathing, brainstem reflexes and coma with an identified cause



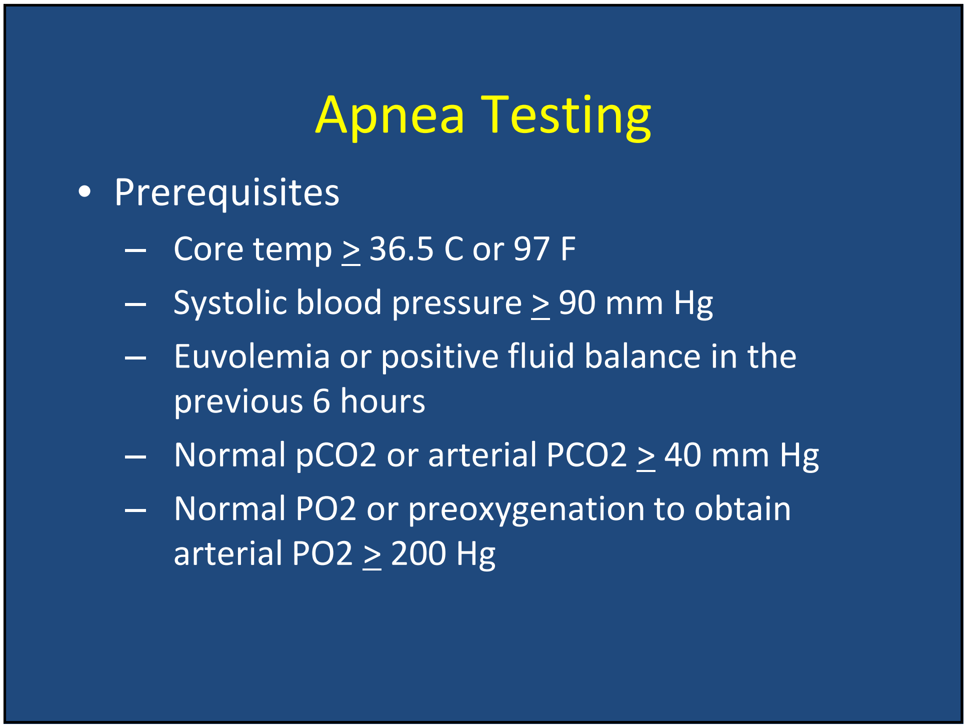
Clinical Evaluation of Brain Death:

- No Cerebral Response to Painful Stimulus
  - Spinal reflexes permitted but no posturing allowed
- Absence of Brainstem Function
  - Tested by Cranial Nerve Examination
  - Interval Between Exams Arbitrary, Often 6 Hours
  - Adequate Vital Signs Required
    - SpO2 over 90%
    - SBP over 90 mmHg
- Apnea Examination
- (Clinical examinations performed twice and apnea testing occurs once)



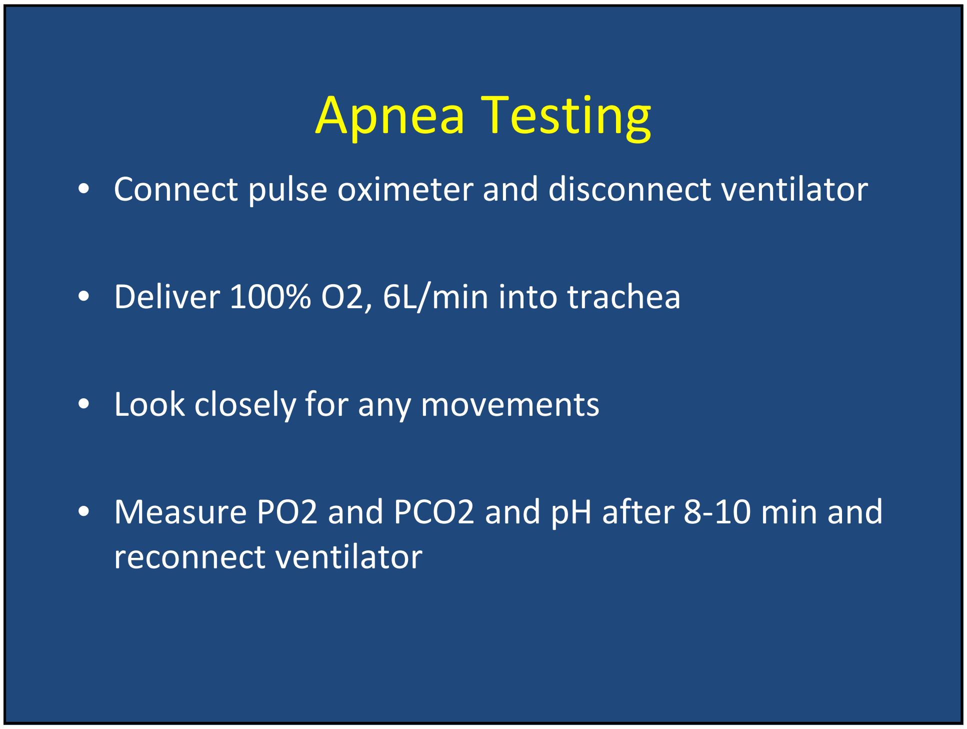
The Core of the Examination

- **Part I: Coma**
- **Part II: Absence of brainstem reflexes**
  - Pupillary Response to Light
  - Corneal Reflex
  - Gag Reflex
  - Cough Reflex
  - Occulocephalic Reflex (Dolls Eyes)/ Occulovestibular Reflex (Cold Calorics)
- **Part III: Apnea (inferior brainstem)**



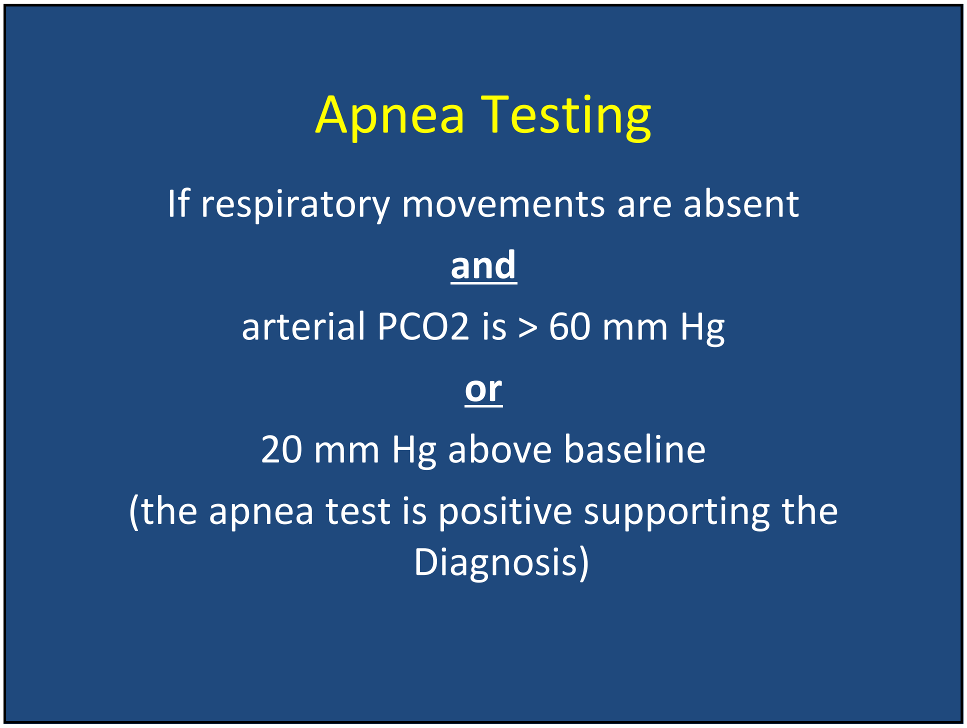
Apnea Testing

- Prerequisites
  - Core temp ≥ 36.5 C or 97 F
  - Systolic blood pressure ≥ 90 mm Hg
  - Euvolemia or positive fluid balance in the previous 6 hours
  - Normal pCO2 or arterial PCO2 ≥ 40 mm Hg
  - Normal PO2 or preoxygenation to obtain arterial PO2 ≥ 200 Hg



Apnea Testing

- Connect pulse oximeter and disconnect ventilator
- Deliver 100% O2, 6L/min into trachea
- Look closely for any movements
- Measure PO2 and PCO2 and pH after 8-10 min and reconnect ventilator



Apnea Testing

If respiratory movements are absent

and

arterial PCO2 is > 60 mm Hg

or

20 mm Hg above baseline

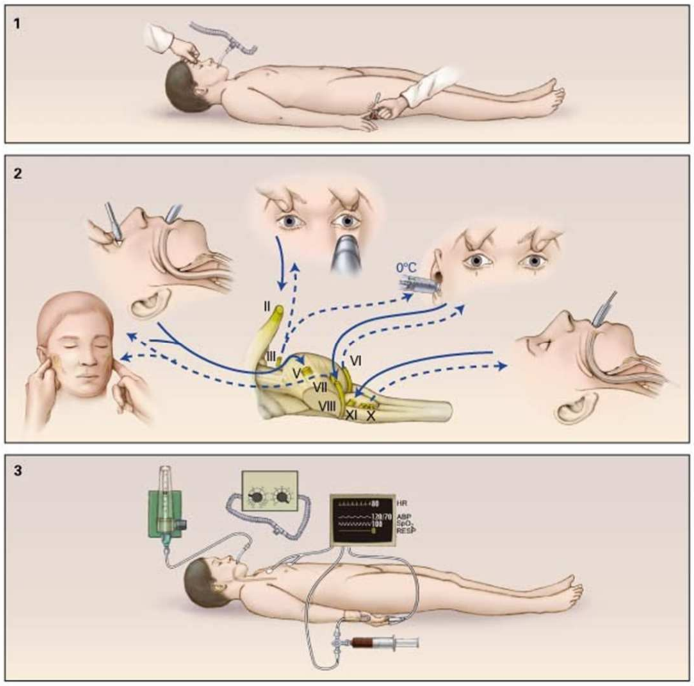
(the apnea test is positive supporting the Diagnosis)

Apnea Testing

- Connect ventilator, if:
  - SBP < 90 mmHg
  - Significant O2 desaturation and cardiac arrhythmias are present
  - Immediately send ABG

Prerequisites to rule out

- Severe electrolyte imbalance
- Acid-base or endocrine disturbance
- Hypothermia (< 32 ^{o}C or lower)
- Hypotension
- Absence of evidence drug intoxication, poisoning, or neuromuscular blocking agents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N Engl J Med 344:1215, April 19, 2001

Ancillary Tests

Vascular

- Cerebral angiography
- Cerebral blood flow scan
- Transcranial Doppler ultrasonography

Functional

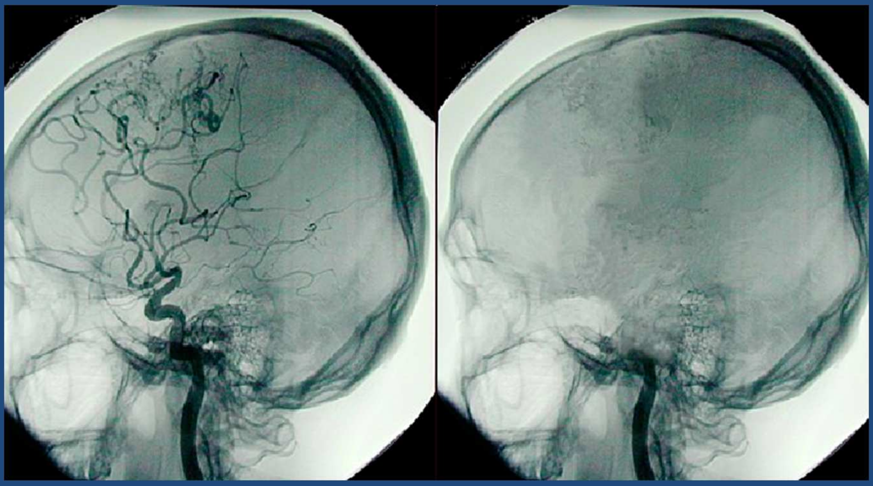
- Electrocenphalography (EEG)

Cerebral Angiography

- Absence of Filling Beyond the Circle of Willis
- Pro: Considered "Gold Standard" in Diagnosis of brain death[1]
- Con: Requires extensive, specific manpower, transport out of ICU

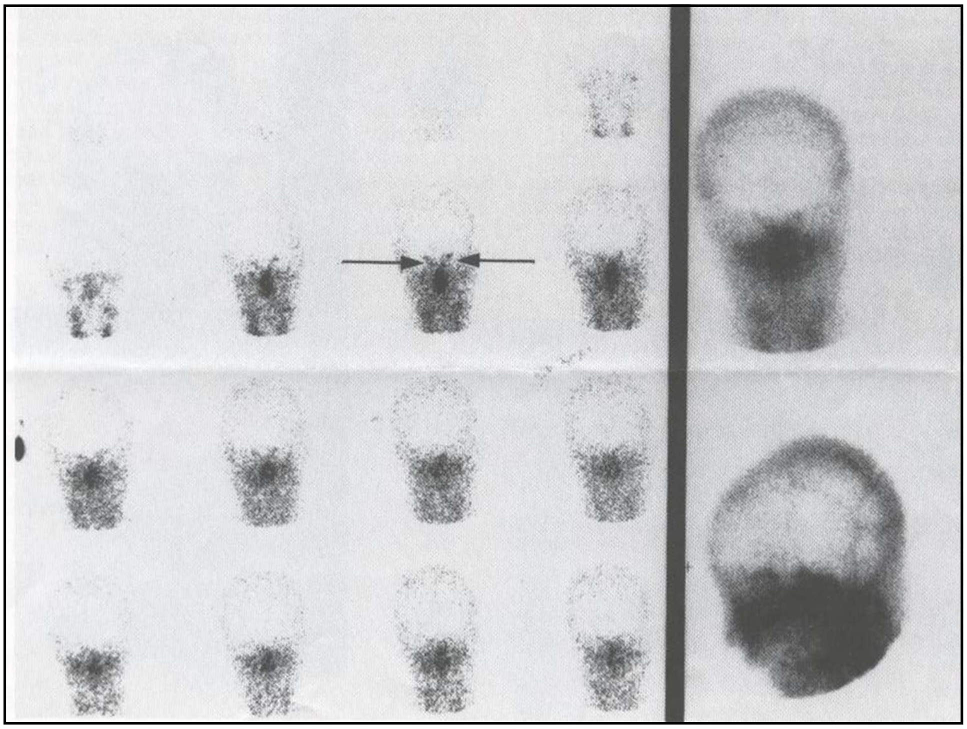
1.Morenski JD, et al. J Int Care Med 2003;18(4):211-221

Cerebral angiogram



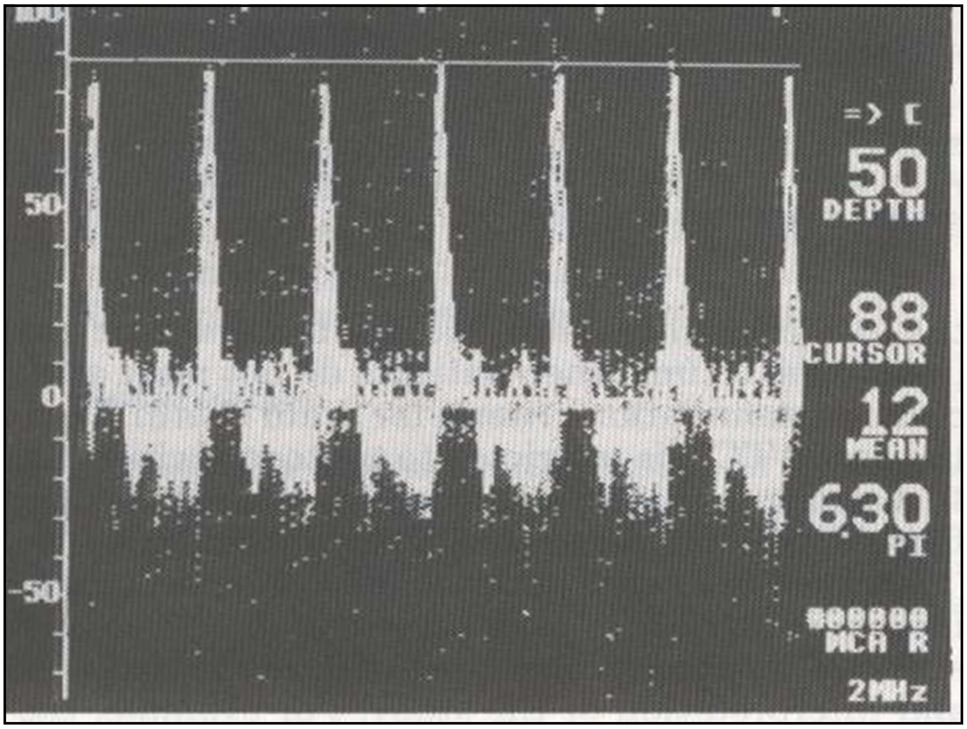
Cerebral Blood Flow Scan

- Technetium-99 Radioisotope study
- Pro: Can be done bedside
- Con: Requires specific manpower, poor sensitivity on posterior circulation



Transcranial Doppler Ultrasonography

- Absence of diastolic flow, reverberating flow indicates high ICP
- Con: Many patients lack adequate insonation windows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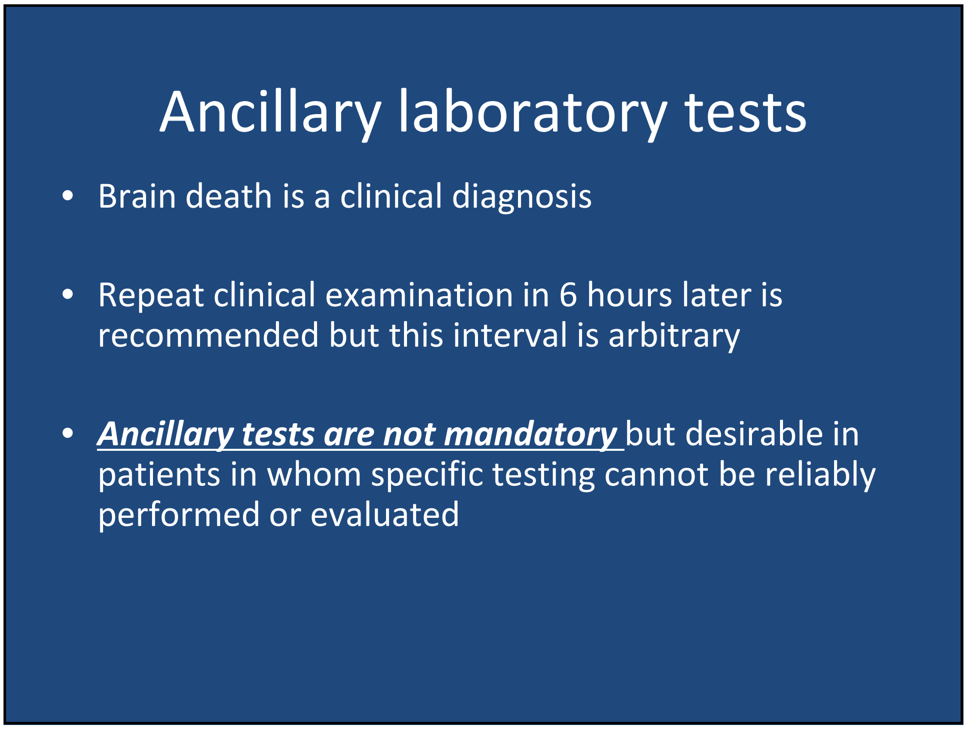
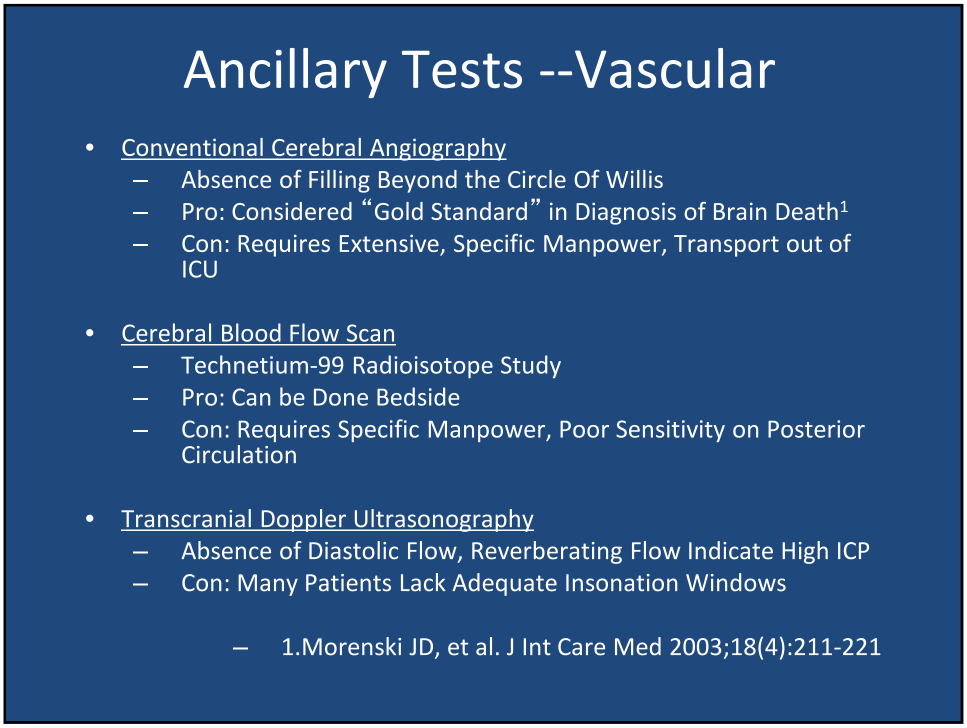


Ancillary laboratory tests

- Brain death is a clinical diagnosis
- Repeat clinical examination in 6 hours later is recommended but this interval is arbitrary
- ***Ancillary tests are not mandatory*** but desirable in patients in whom specific testing cannot be reliably performed or evaluated



Ancillary Tests --Vascular

- Conventional Cerebral Angiography
  - Absence of Filling Beyond the Circle Of Willis
  - Pro: Considered "Gold Standard" in Diagnosis of Brain Death[1]
  - Con: Requires Extensive, Specific Manpower, Transport out of ICU
- Cerebral Blood Flow Scan
  - Technetium-99 Radioisotope Study
  - Pro: Can be Done Bedside
  - Con: Requires Specific Manpower, Poor Sensitivity on Posterior Circulation
- Transcranial Doppler Ultrasonography
  - Absence of Diastolic Flow, Reverberating Flow Indicate High ICP
  - Con: Many Patients Lack Adequate Insonation Windows

  - 1.Morenski JD, et al. J Int Care Med 2003;18(4):211-221

Ancillary Tests -- Functional

- Electroencephalography (EEG)
  - Absence of Electrical Activity for 30 Minutes
  - Specific Criteria For Sensitivity of Recording
  - Pro: Noninvasive, Readily Available
  - Con: Significant Interference from ICU Devices

- Somatosensory Evoked Potentials
  - Absence of N20-P22 Response from Median Nerve Stimulation Commonly Used
  - Pro: Relatively Widely Available
  - Con: Confounded by Nerve Injury, Tests Limited Regions of Brain

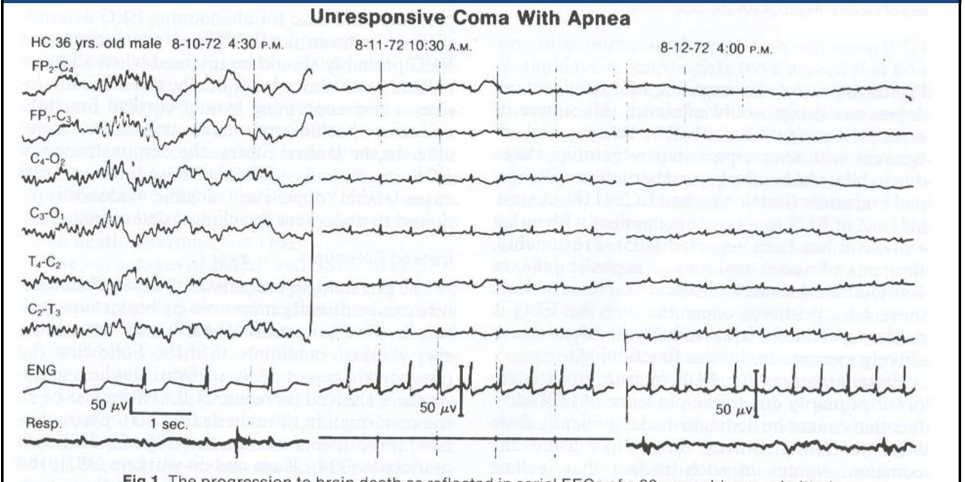


Fig 1. The progression to brain death as reflected in serial EEGs of a 36-year-old man admitted

Brain Death around the World

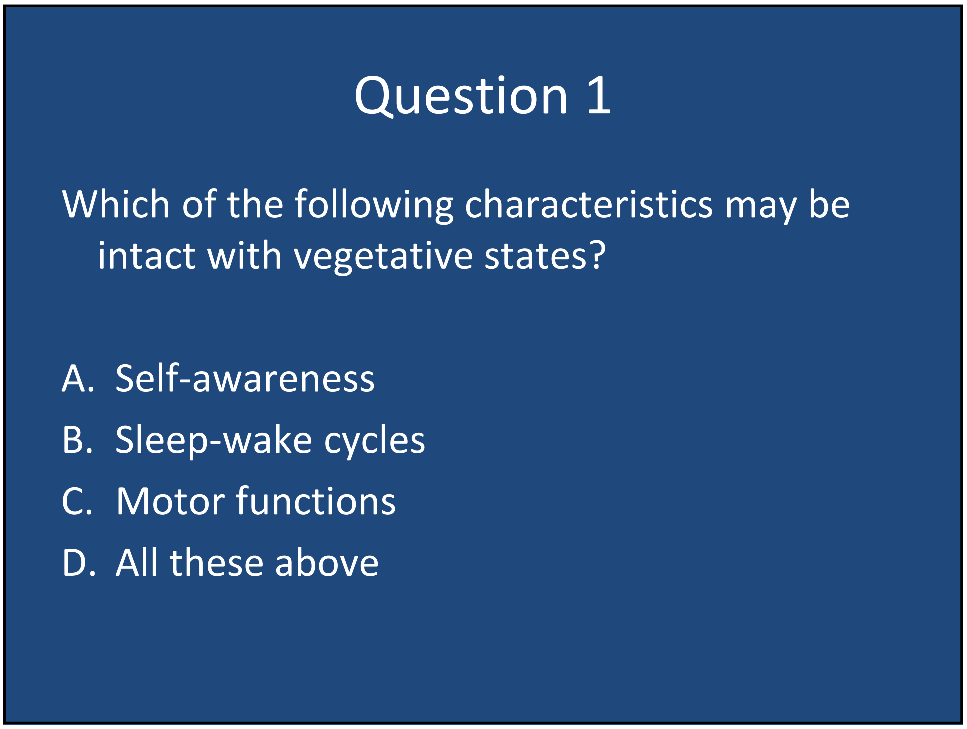
Wijdicks EFM. Brain death worldwide: Accepted fact but no global consensus in diagnostic criteria NEUROLOGY 2002;58:20-25

- Guidelines of 80 countries reviewed
- Legal standards on organ transplantation present in 69% (55 of 80 countries)
- Practice guidelines for brain death for adults in 88%
  - 50% guidelines require >1 physician to declare
  - All guidelines specified exclusion of confounders, presence of irreversible coma, absent motor response, and absent brainstem reflexes
  - Apnea testing required in 59%
  - differences in time of observation and required expertise of examining physicians
  - Confirmatory laboratory testing mandatory in 28 of 70 (40%) guidelines

Approach to the coma patient

Summary

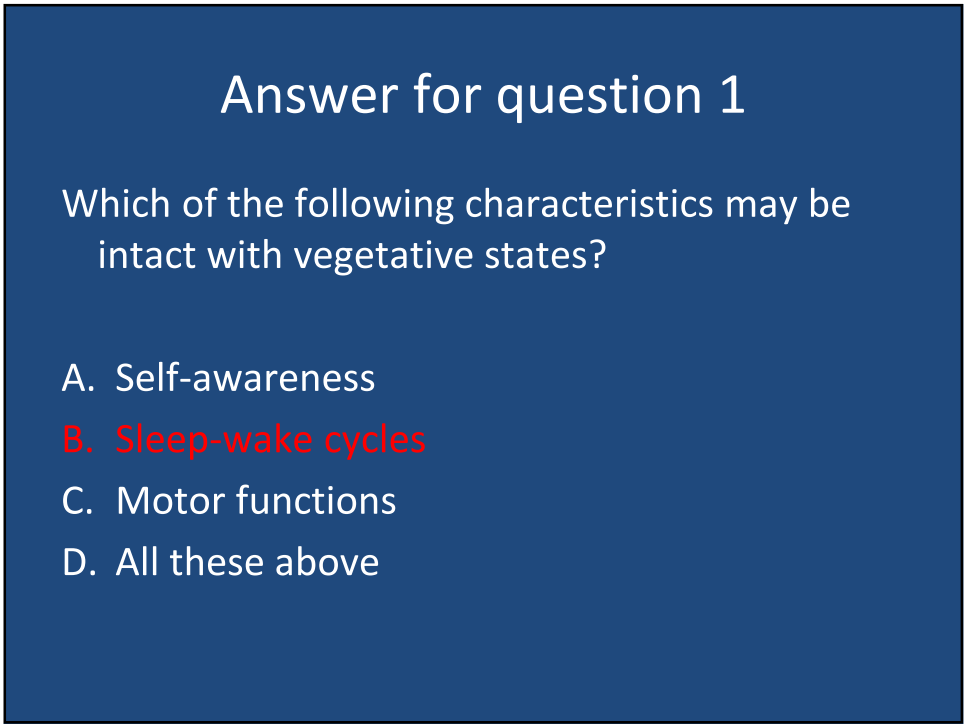
- Review Consciousness and Coma Pathophysiology
- Discuss major syndromes of impaired states of consciousness
- Review the examination of the comatose patient
- Discuss the “complete comatose examination – Brain Death”



Question 1

Which of the following characteristics may be intact with vegetative states?

A. Self-awareness
B. Sleep-wake cycles
C. Motor functions
D. All these above



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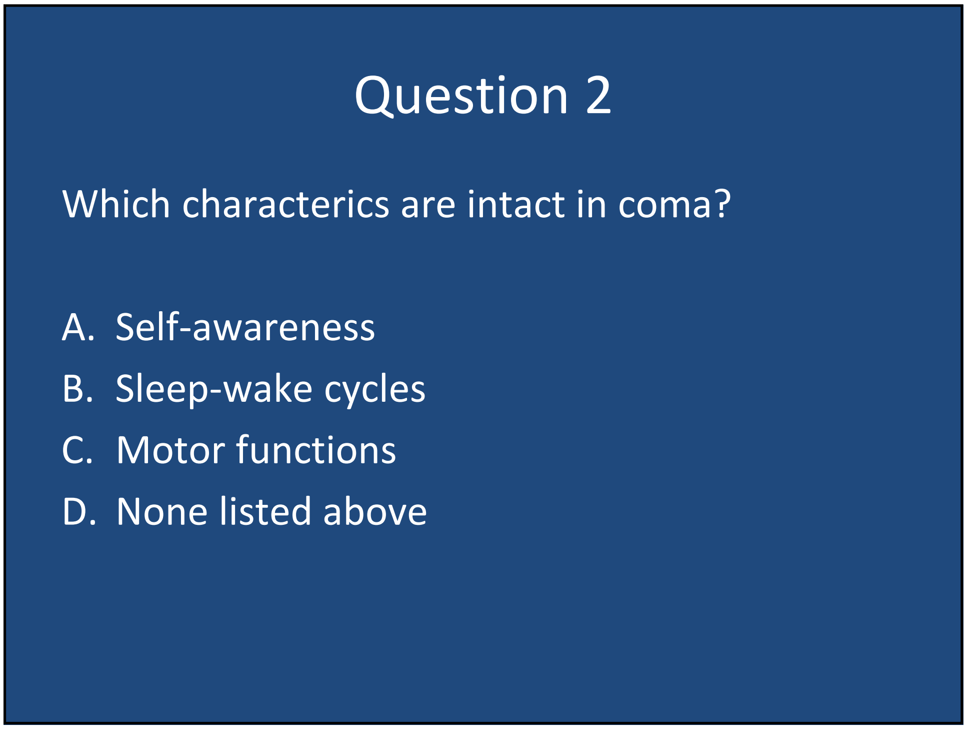
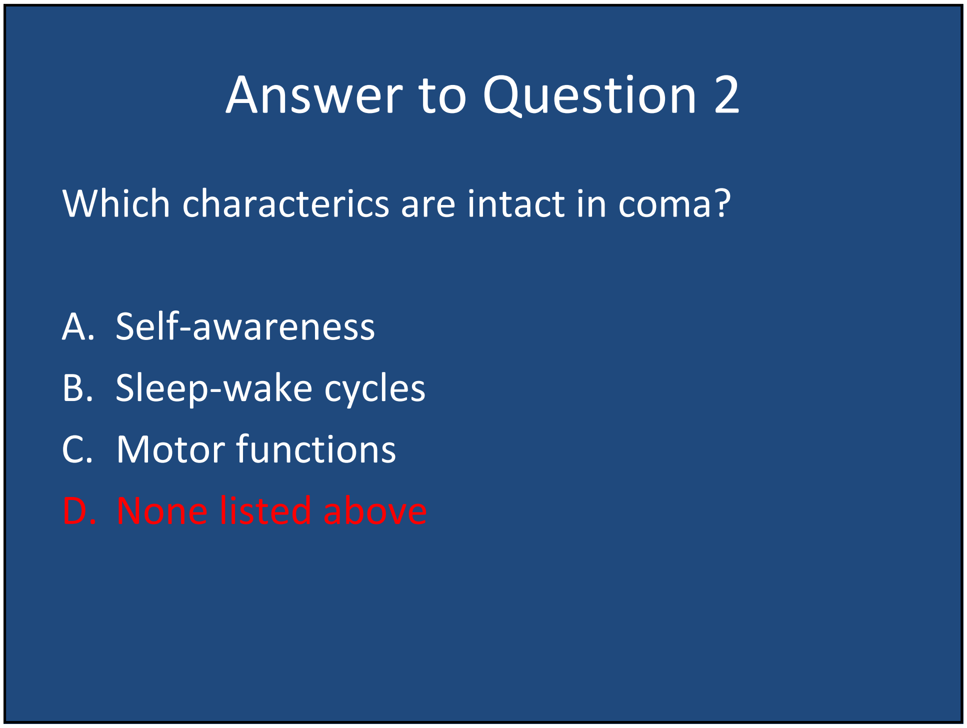


Question 2

Which characterics are intact in coma?

A. Self-awareness
B. Sleep-wake cycles
C. Motor functions
D. None listed above



Answer to Question 2

Which characterics are intact in coma?

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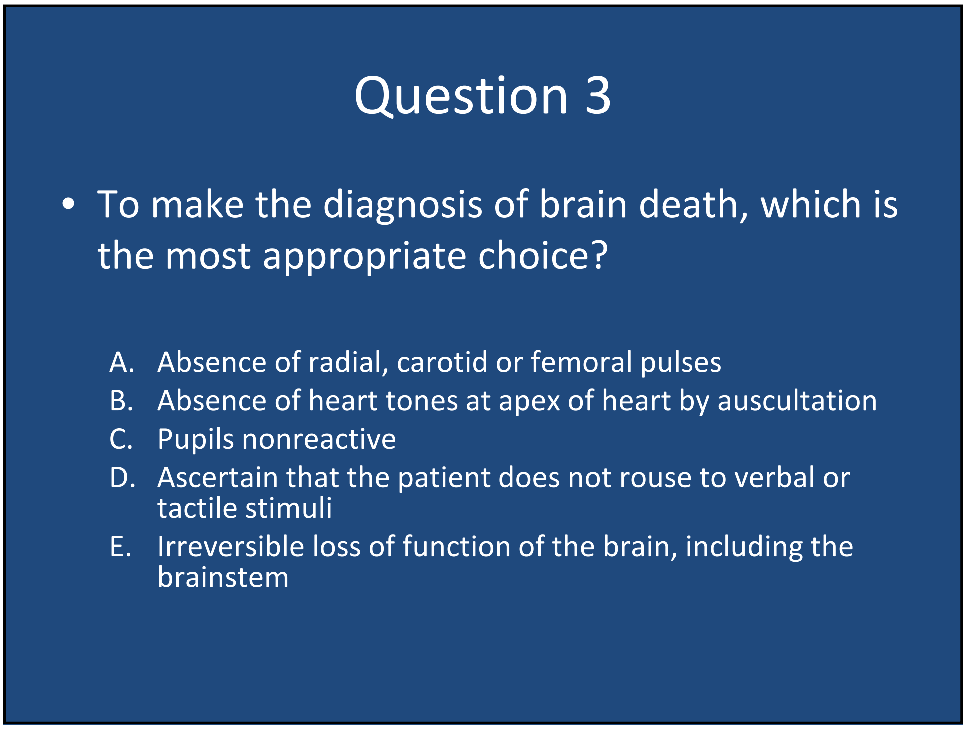
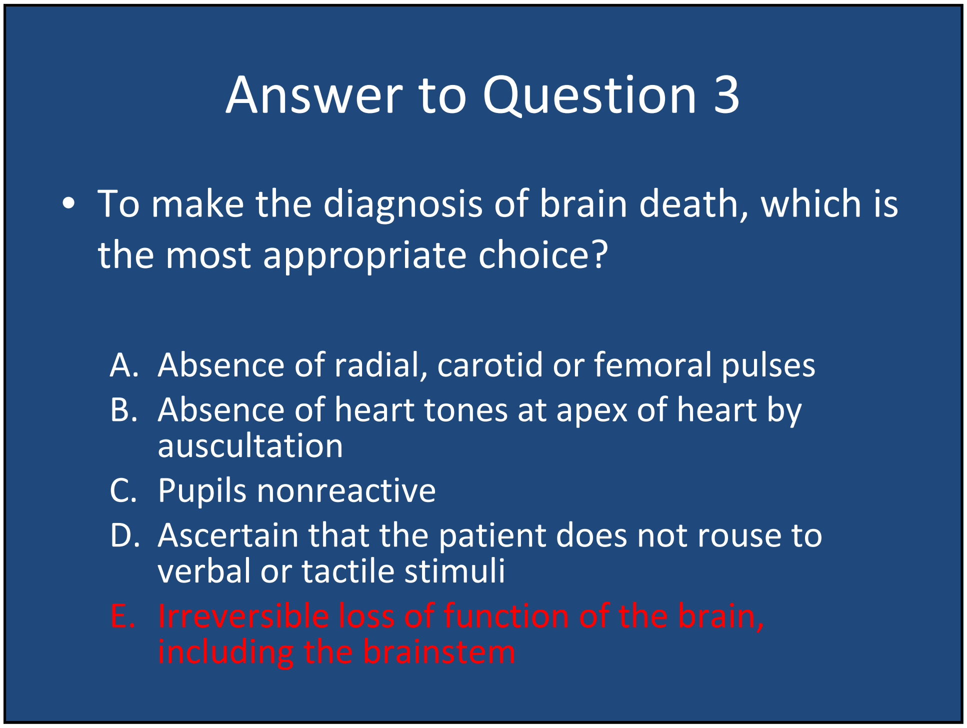
D. None listed above



Question 3

- To make the diagnosis of brain death, which is the most appropriate choice?

A. Absence of radial, carotid or femoral pulses
B. Absence of heart tones at apex of heart by auscultation
C. Pupils nonreactive
D. Ascertain that the patient does not rouse to verbal or tactile stimuli
E. Irreversible loss of function of the brain, including the brainstem



Answer to Question 3

- To make the diagnosis of brain death, which is the most appropriate choice?

A. Absence of radial, carotid or femoral pulses
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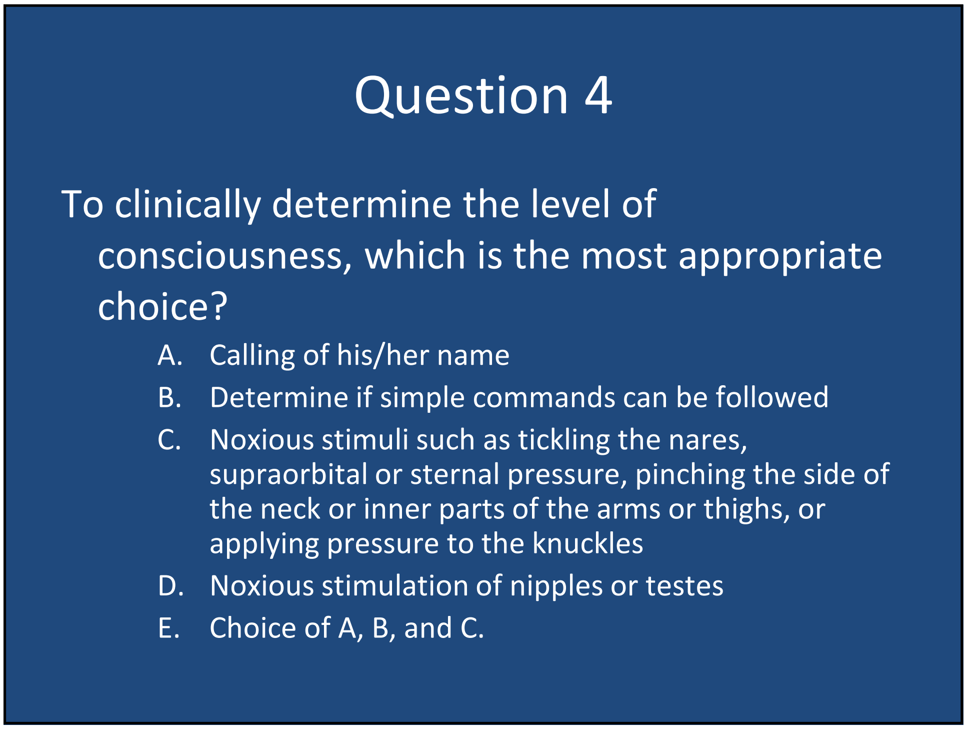
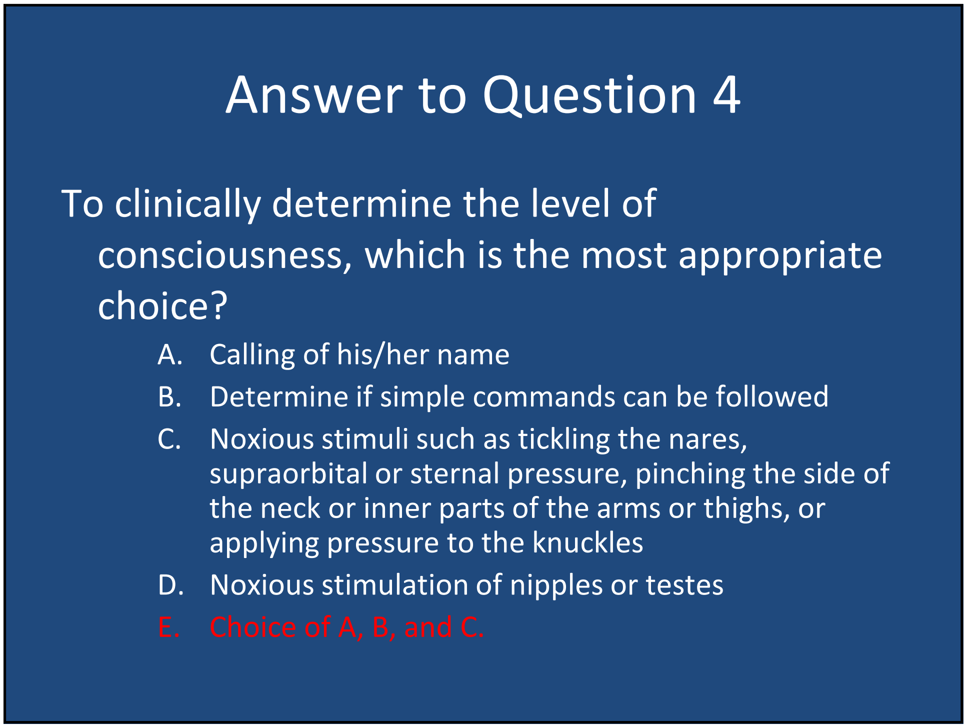


Question 4

To clinically determine the level of consciousness, which is the most appropriate choice?

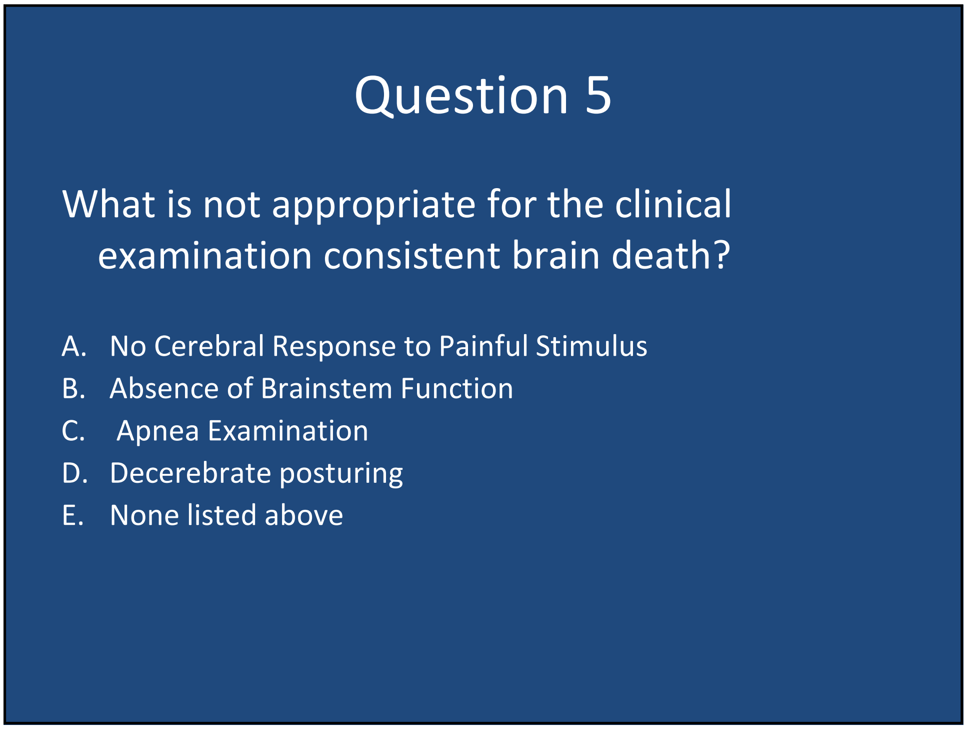
A. Calling of his/her name
B. Determine if simple commands can be followed
C. Noxious stimuli such as tickling the nares, supraorbital or sternal pressure, pinching the side of the neck or inner parts of the arms or thighs, or applying pressure to the knuckles
D. Noxious stimulation of nipples or testes
E. Choice of A, B, and C.



Answer to Question 4

To clinically determine the level of consciousness, which is the most appropriate choice?

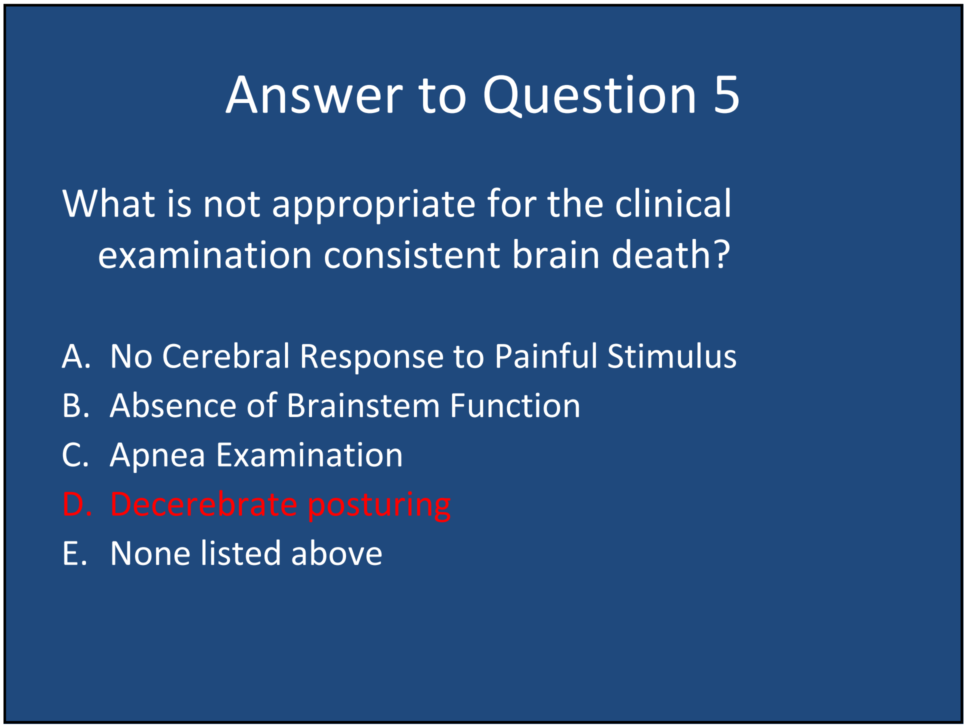
A. Calling of his/her name
B. Determine if simple commands can be followed
C. Noxious stimuli such as tickling the nares, supraorbital or sternal pressure, pinching the side of the neck or inner parts of the arms or thighs, or applying pressure to the knuckles
D. Noxious stimulation of nipples or testes
E. Choice of A, B, and C.



Question 5

What is not appropriate for the clinical examination consistent brain death?

A. No Cerebral Response to Painful Stimulus
B. Absence of Brainstem Function
C. Apnea Examination
D. Decerebrate posturing
E. None listed above

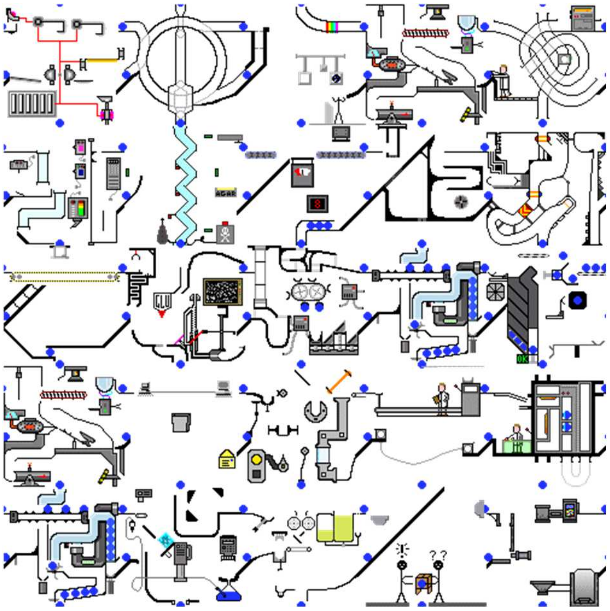


Answer to Question 5

What is not appropriate for the clinical examination consistent brain death?

A. No Cerebral Response to Painful Stimulus
B. Absence of Brainstem Function
C. Apnea Examination
D. Decerebrate posturing
E. None listed above

Thank you for your Attention



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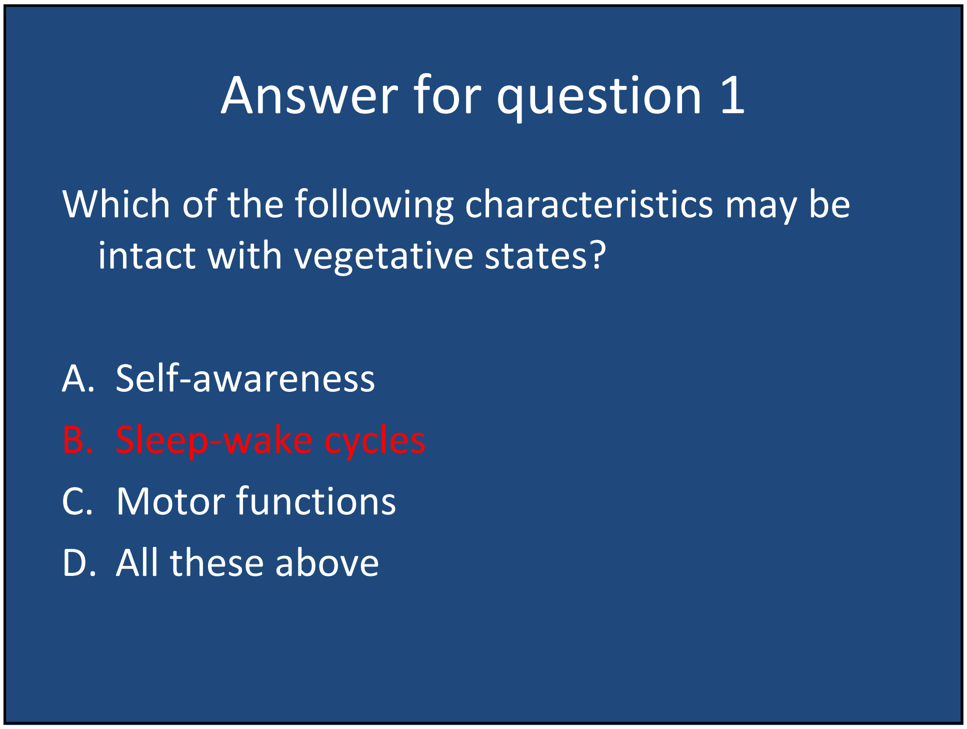

Answer for question 1

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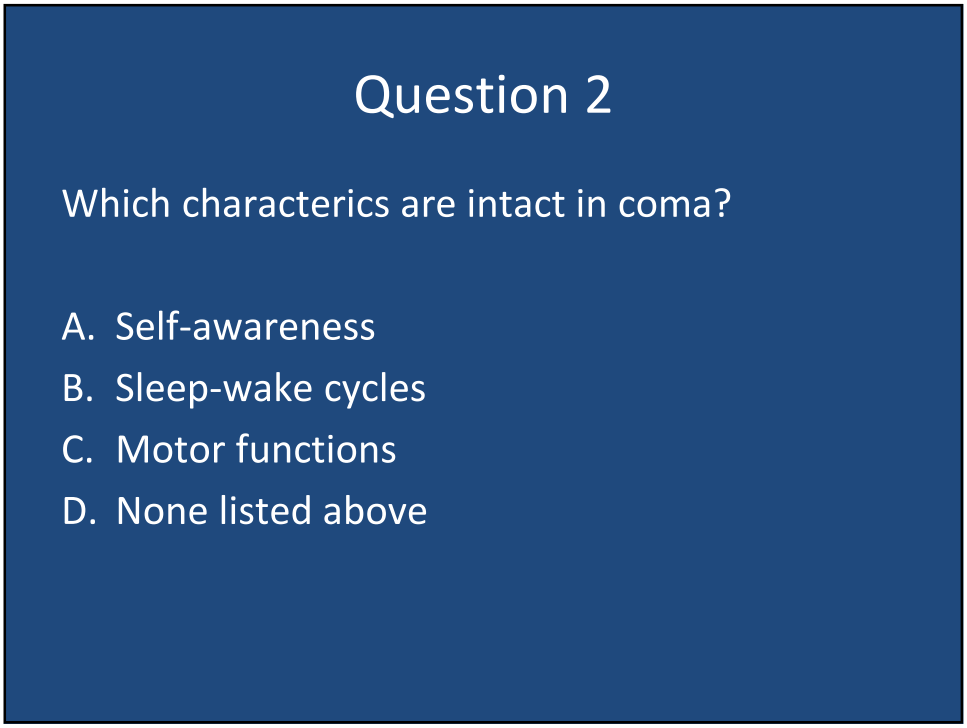
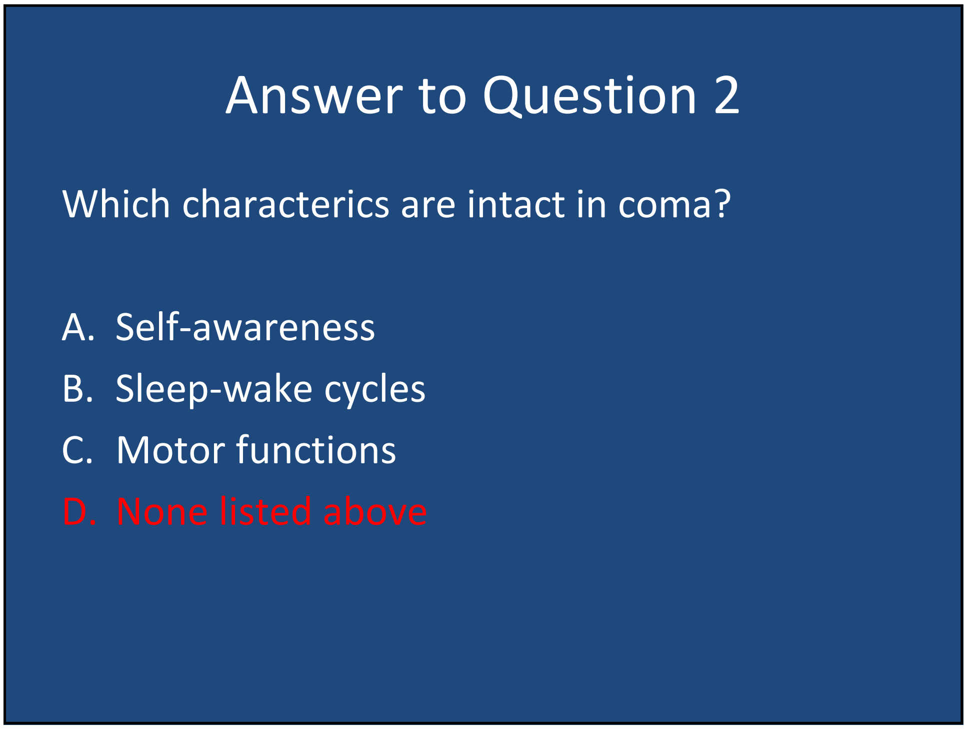


Question 2

Which characterics are intact in coma?

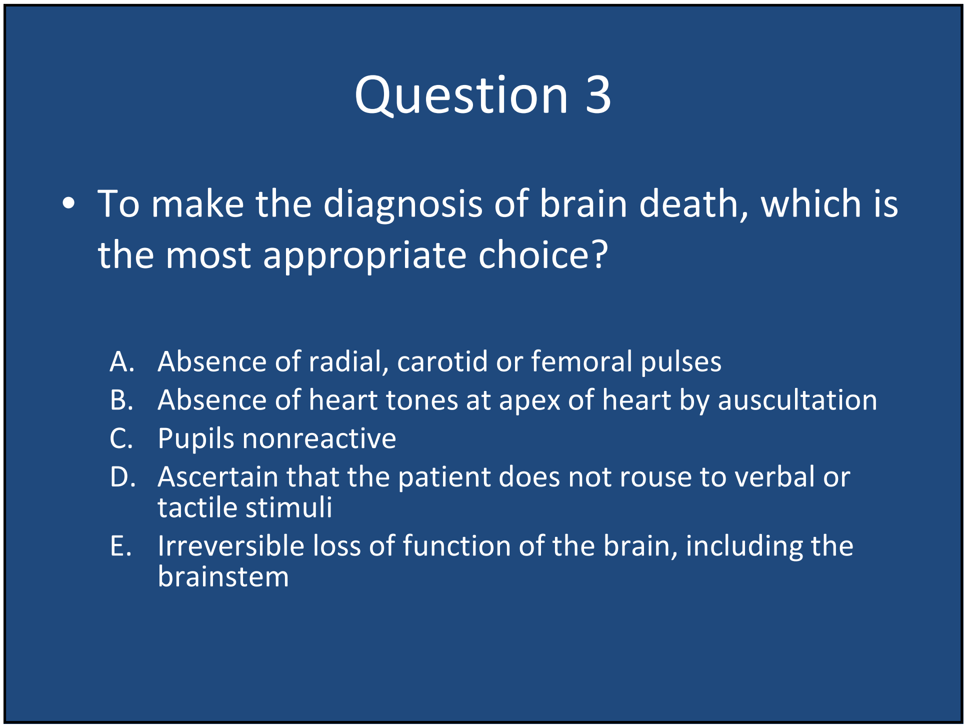
A. Self-awareness
B. Sleep-wake cycles
C. Motor functions
D. None listed above



Answer to Question 2

Which characterics are intact in coma?

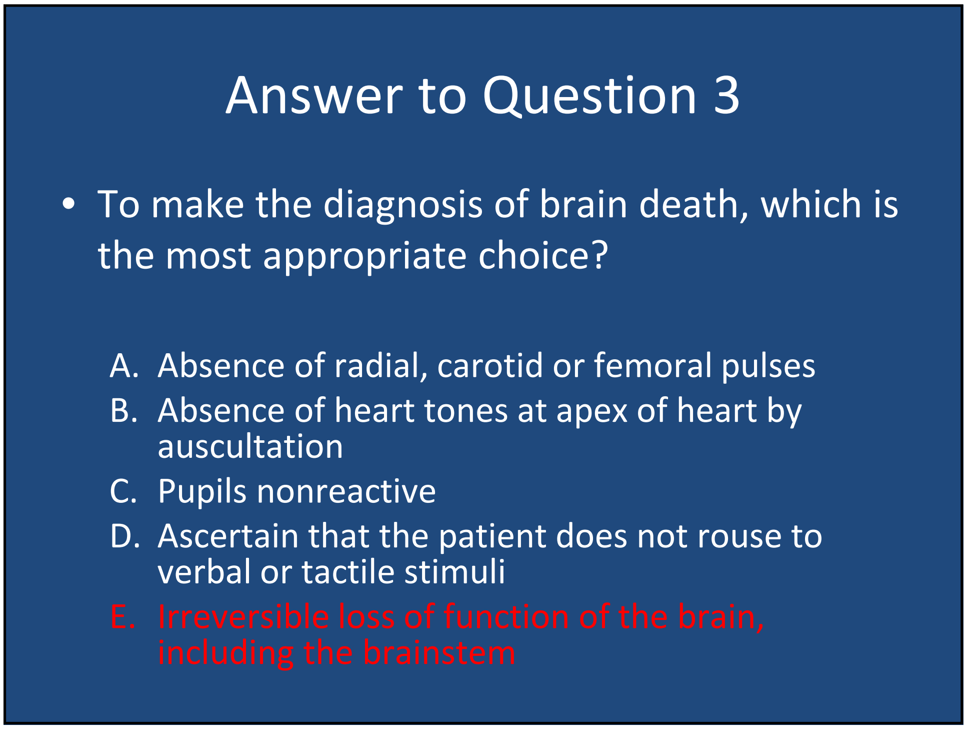
A. Self-awareness
B. Sleep-wake cycles
C. Motor functions
D. None listed above



Question 3

- To make the diagnosis of brain death, which is the most appropriate choice?

A. Absence of radial, carotid or femoral pulses
B. Absence of heart tones at apex of heart by auscultation
C. Pupils nonreactive
D. Ascertain that the patient does not rouse to verbal or tactile stimuli
E. Irreversible loss of function of the brain, including the brainstem



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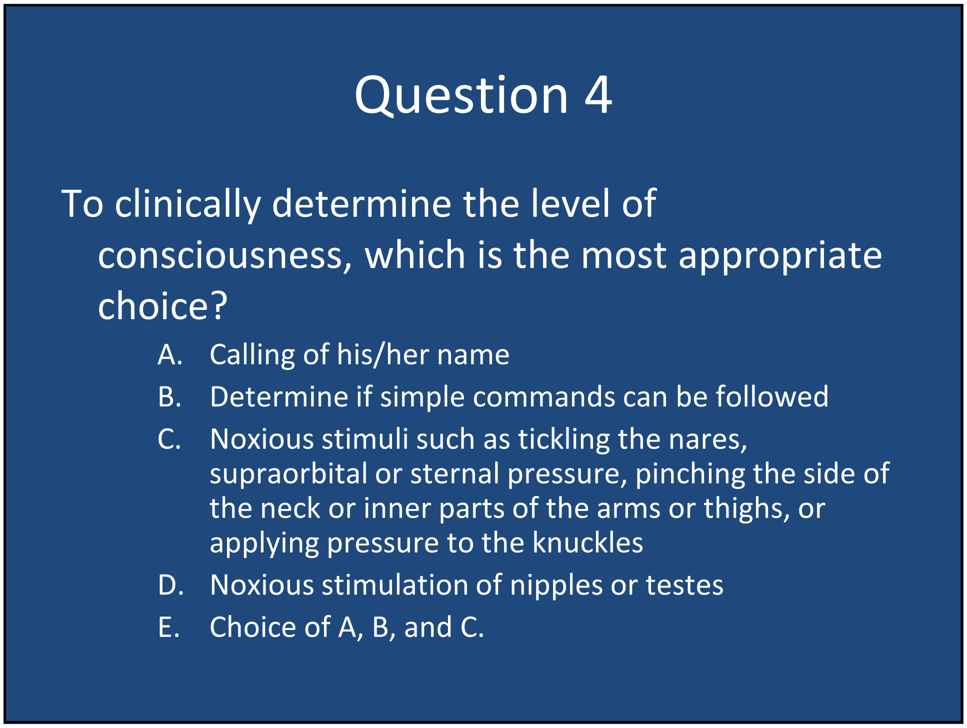

Question 4

To clinically determine the level of consciousness, which is the most appropriate choice?

A. Calling of his/her name
B. Determine if simple commands can be followed
C. Noxious stimuli such as tickling the nares, supraorbital or sternal pressure, pinching the side of the neck or inner parts of the arms or thighs, or applying pressure to the knuckles
D. Noxious stimulation of nipples or testes
E. Choice of A, B, and C.

Answer to Question 4

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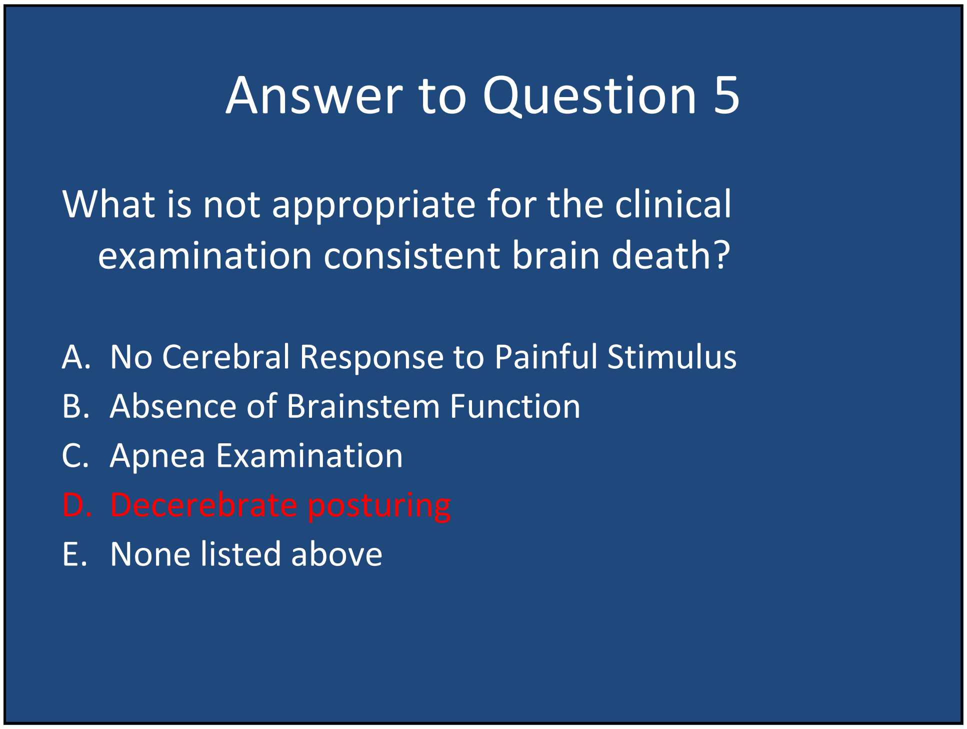
Question 5

What is not appropriate for the clinical examination consistent brain death?

A. No Cerebral Response to Painful Stimulus
B. Absence of Brainstem Function
C. Apnea Examination
D. Decerebrate posturing
E. None listed above



Answer to Question 5

What is not appropriate for the clinical examination consistent brain death?

A. No Cerebral Response to Painful Stimulus
B. Absence of Brainstem Function
C. Apnea Examination
D. Decerebrate posturing
E. None listed above

Transfusion Practices in the ICU

James Rawn, MD
Instructor in Surgery, Harvard Medical School
Director of Quality Outcomes
Cardiac Surgery ICU
Division of Cardiac Surgery
Brigham and Women’s Hospital

No conflicts to report

Anemia is associated with poor clinical outcomes.

But…

There is little definitive evidence that blood transfusion is safe and effective therapy for anemia when standard transfusion thresholds are used.

"A great deal is known with regard to blood transfusion risks yet little is known of its benefits."

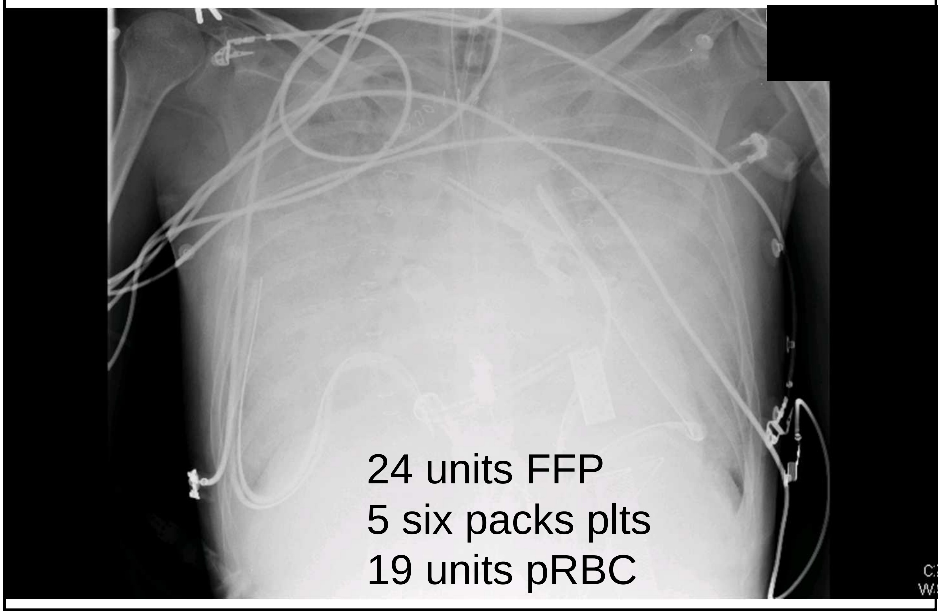
Report From the STS Workforce on Evidence Based Surgery

Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline

Risks of Blood Transfusion

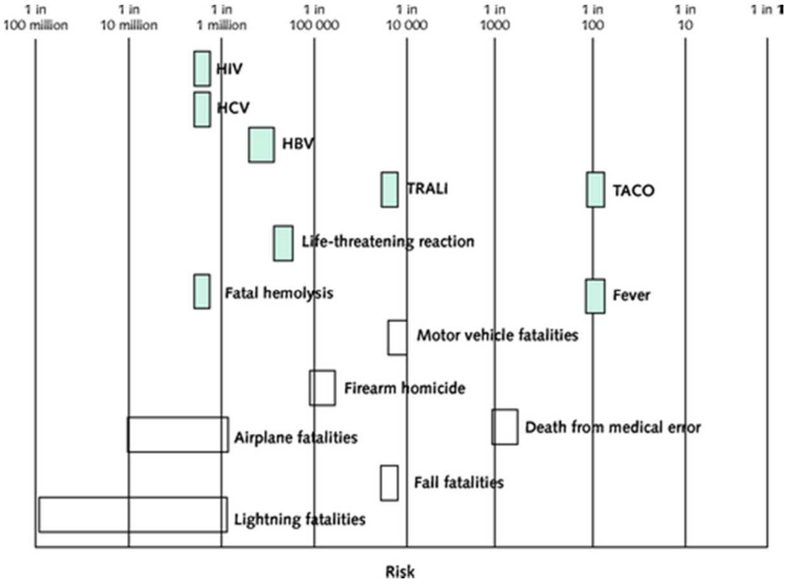
- Infectious
- Immunologic
- Other morbidity and mortality
- Historically, we have underrated the magnitude of transfusion risk

Transfusion Related Acute Lung Injury



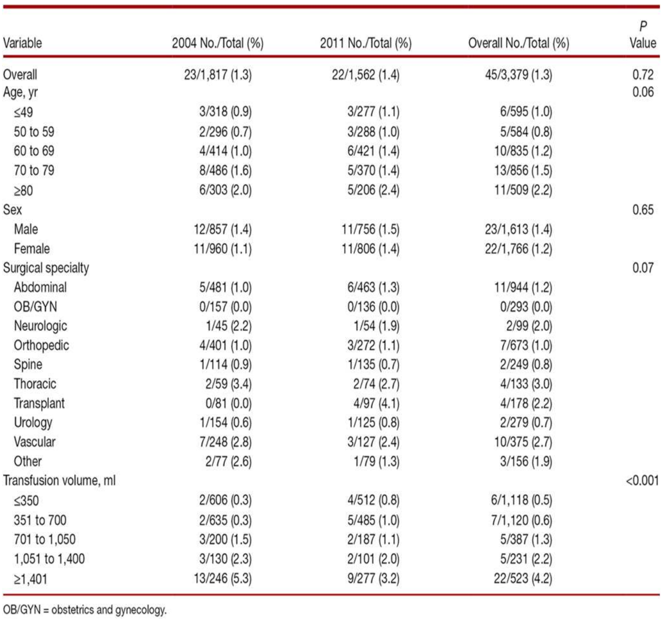
24 units FFP
5 six packs plts
19 units pRBC

Annals of Internal Medicine
Established in 1927 by the American College of Physicians



Ann Intern Med. 2012;157(1):49-58. doi:10.7326/0003-4819-157-1-201206190-00429

Incidence of TRALI may be 100 fold greater than previous estimates



Variable	2004 No./Total (%)	2011 No./Total (%)	Overall No./Total (%)	*P* Value
Overall	23/1,817 (1.3)	22/1,562 (1.4)	45/3,379 (1.3)	0.72
Age, yr				0.06
≤49	3/318 (0.9)	3/277 (1.1)	6/595 (1.0)	
50 to 59	2/296 (0.7)	3/288 (1.0)	5/584 (0.8)	
60 to 69	4/414 (1.0)	6/421 (1.4)	10/835 (1.2)	
70 to 79	8/486 (1.6)	5/370 (1.4)	13/856 (1.5)	
≥80	6/303 (2.0)	5/206 (2.4)	11/509 (2.2)	
Sex				0.65
Male	12/857 (1.4)	11/756 (1.5)	23/1,613 (1.4)	
Female	11/960 (1.1)	11/806 (1.4)	22/1,766 (1.2)	
Surgical specialty				0.07
Abdominal	5/481 (1.0)	6/463 (1.3)	11/944 (1.2)	
OB/GYN	0/157 (0.0)	0/136 (0.0)	0/293 (0.0)	
Neurologic	1/45 (2.2)	1/54 (1.9)	2/99 (2.0)	
Orthopedic	4/401 (1.0)	3/272 (1.1)	7/673 (1.0)	
Spine	1/114 (0.9)	1/135 (0.7)	2/249 (0.8)	
Thoracic	2/59 (3.4)	2/74 (2.7)	4/133 (3.0)	
Transplant	0/81 (0.0)	4/97 (4.1)	4/178 (2.2)	
Urology	1/154 (0.6)	1/125 (0.8)	2/279 (0.7)	
Vascular	7/248 (2.8)	3/127 (2.4)	10/375 (2.7)	
Other	2/77 (2.6)	1/79 (1.3)	3/156 (1.9)	
Transfusion volume, ml				<0.001
≤350	2/606 (0.3)	4/512 (0.8)	6/1,118 (0.5)	
351 to 700	2/635 (0.3)	5/485 (1.0)	7/1,120 (0.6)	
701 to 1,050	3/200 (1.5)	2/187 (1.1)	5/387 (1.3)	
1,051 to 1,400	3/130 (2.3)	2/101 (2.0)	5/231 (2.2)	
≥1,401	13/246 (5.3)	9/277 (3.2)	22/523 (4.2)	

OB/GYN = obstetrics and gynecology.

From: Characterizing the Epidemiology of Postoperative Transfusion-related Acute Lung Injury
Anesthesiology. 2015;122(1):12-20. doi:10.1097/ALN.0000000000000514

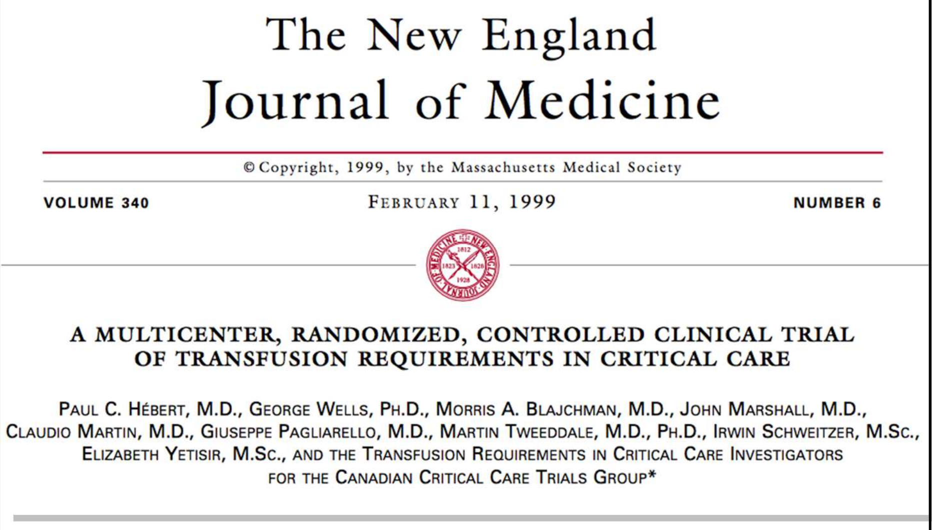
Transfusions in the ICU have been linked to:

- Increased infection
- Increased incidence of reintubation, intubation time and ARDS
- Post bypass myocardial ischemia, LV dysfunction, atrial arrhythmias
- Renal failure, stroke
- Death

Blood Transfusion

- appears to be proinflammatory.
- appears to be immunosuppressive.
- does not appear to significantly improve oxygen delivery to tissues acutely.

The value of restrictive transfusion stategies was suggested by the TRICC trial.



The New England
Journal of Medicine

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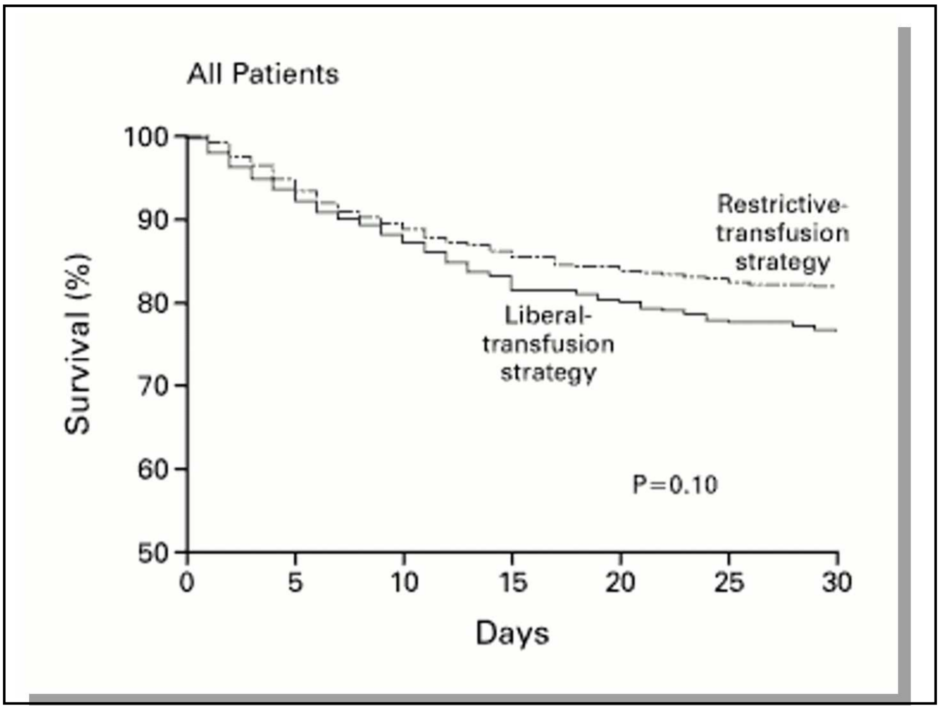
VOLUME 340 FEBRUARY 11, 1999 NUMBER 6

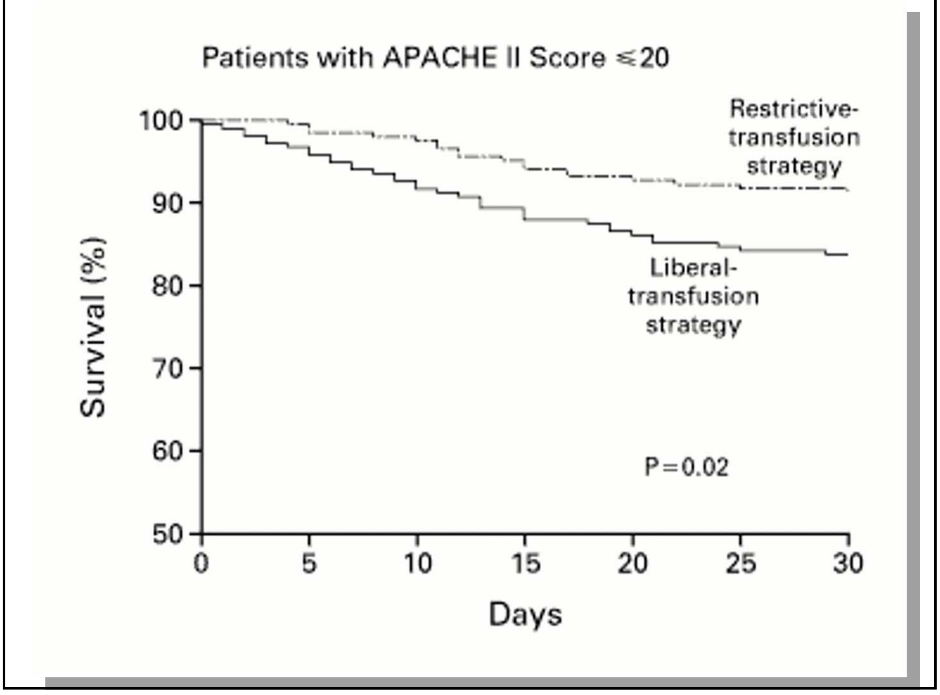
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

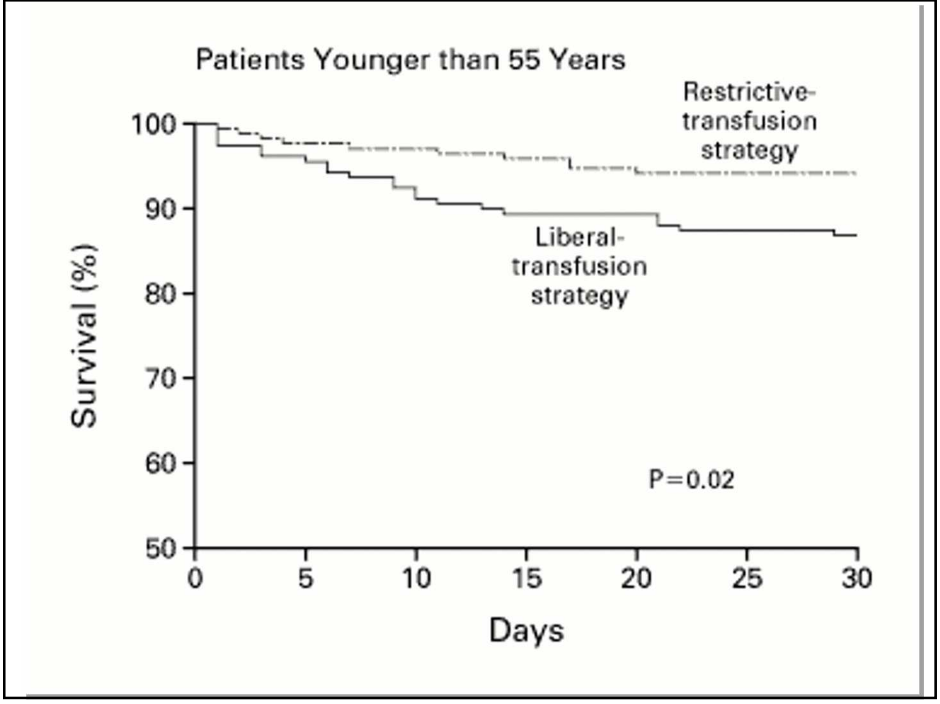
PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

Transfusion Strategies

- Liberal Strategy
  Transfuse for Hb < 10 g/dL
- Restrictive Strategy
  Transfuse for Hb < 7 g/dL




Patients with APACHE II Score ≤20
Restrictive-transfusion strategy
Liberal-transfusion strategy
Survival (%)
100
90
80
70
60
50
0
5
10
15
20
25
30
Days
P=0.02


Patients Younger than 55 Years
Restrictive-transfusion strategy
Liberal-transfusion strategy
Survival (%)
100
90
80
70
60
50
0
5
10
15
20
25
30
Days
P=0.02

Retrospective Studies

Perioperative Blood Transfusion Is Associated With Worse Clinical Outcomes in Resected Lung Cancer Ting Wang, MD, Lili Luo, MD, He Huang, MD, Jingrui Yu, MD, Changchuan Pan, MD, Xiaohong Cai, MD, Bin Hu, MD, Xude Yin, MD The Annals of Thoracic Surgery Volume 97, Issue 5, May 2014, Pages 1827–1837

The deleterious effect of perioperative allogeneic blood transfusion in patients with resected lung cancer has been controversial. We conducted this meta-analysis to answer the question of whether perioperative allogeneic blood transfusion adversely affects recurrence and survival in patients with resected lung cancer. Included were 23 studies with 6,474 patients. The result showed allogeneic blood transfusion was significantly associated with earlier recurrence and worse survival in patients with surgically resected lung cancer. We suggest transfusion policy should be stricter in lung cancer patients undergoing resection, especially with early-stage disease. Prospective large-scale studies are still warranted.

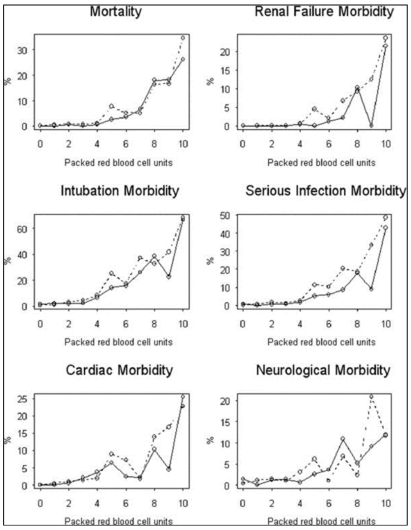
Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting

Colleen Gorman Koch, MD, MS; Liang Li, PhD; Andra I. Duncan, MD; Tomislav Mihaljevic, MD; Delos M. Cosgrove, MD; Floyd D. Loop, MD; Norman J. Starr, MD; Eugene H. Blackstone, MD

Crit Care Med 2006 Vol. 34, No. 6

We report that transfusion of PRBCs is associated with a dose-dependent increased risk for postoperative cardiac complications, serious infection, renal failure, neurologic complications, overall morbidity, prolonged ventilatory support, and in-hospital mortality after isolated CABG. This association remained strong even after adjusting for risk factors known to be associated with adverse outcome after CABG. In every logistic model, transfusion of PRBCs was the most reliable predictor associated with adverse outcome.

Figure 2.



Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting *.
Koch, Colleen; Gorman MD, MS; Li, Liang; Duncan, Andra; Mihaljevic, Tomislav; Cosgrove, Delos; Loop, Floyd; Starr, Norman; Blackstone, Eugene

Critical Care Medicine. 34(6):1608-1616, June 2006.
DOI: 10.1097/01.CCM.0000217920.48559.D8

Figure 2. Unadjusted relationship between units of packed red blood cells, platelet transfusion, and morbidity and mortality outcomes is graphically depicted in this panel. The solid lines represent those patients who received platelet transfusions per unit of packed red blood cells transfused. The dashed lines represent those patients who received only packed red blood cells. As the number of units of blood transfused increases, so does the risk for every postoperative adverse outcome.

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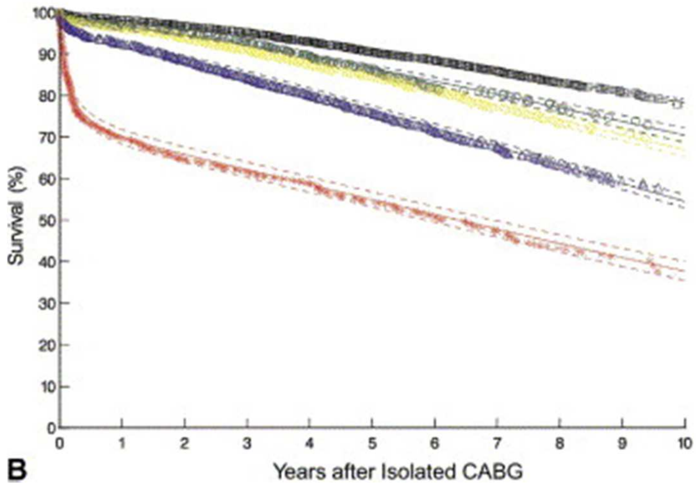
Transfusion in Coronary Artery Bypass Grafting is Associated with Reduced Long-Term Survival

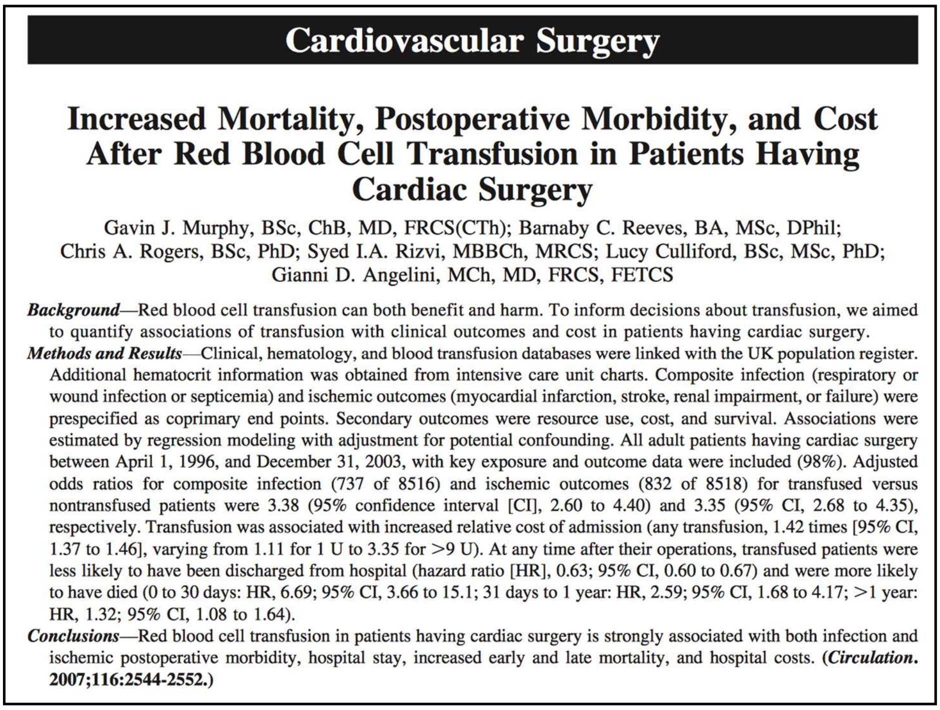
Colleen Gorman Koch, MD, MS, Liang Li, PhD, Andra I. Duncan, MD,
Tomislav Mihaljevic, MD, Floyd D. Loop, MD, Norman J. Starr, MD, and
Eugene H. Blackstone, MD
Departments of Cardiothoracic Anesthesia, Quantitative Health Sciences, and Thoracic and Cardiovascular Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio

The Annals of Thoracic Surgery Volume 81, Issue 5, May 2006, Pages 1650-1657

Survival among transfused patients was significantly reduced as compared with nontransfused patients. The instantaneous risk of death displayed a biphasic pattern: a declining hazard phase from the time of the operation (early hazard) up until 6 months postoperatively and then a late hazard that continued out until about 10 years. Transfusion of red cells was associated with a risk-adjusted reduction in survival for both the early (0.34 ± 0.02, *p* < 0.0001) and late phases (0.074 ± 0.016, *p* < 0.0001).



Black, no blood transfusion; green, 1 unit; yellow, 2 units; blue 3–5 units; and red ≥ 6 units of red blood cells transfused



Cardiovascular Surgery

Increased Mortality, Postoperative Morbidity, and Cost After Red Blood Cell Transfusion in Patients Having Cardiac Surgery

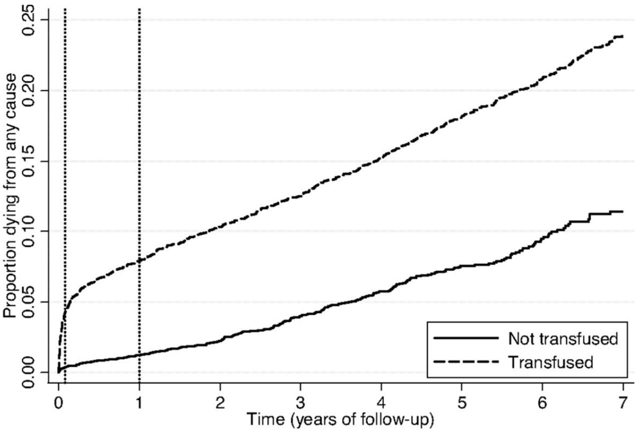
Gavin J. Murphy, BSc, ChB, MD, FRCS(CTh); Barnaby C. Reeves, BA, MSc, DPhil;
Chris A. Rogers, BSc, PhD; Syed I.A. Rizvi, MBBCh, MRCS; Lucy Culliford, BSc, MSc, PhD;
Gianni D. Angelini, MCh, MD, FRCS, FETCS

Background—Red blood cell transfusion can both benefit and harm. To inform decisions about transfusion, we aimed to quantify associations of transfusion with clinical outcomes and cost in patients having cardiac surgery.

Methods and Results—Clinical, hematology, and blood transfusion databases were linked with the UK population register. Additional hematocrit information was obtained from intensive care unit charts. Composite infection (respiratory or wound infection or septicemia) and ischemic outcomes (myocardial infarction, stroke, renal impairment, or failure) were prespecified as coprimary end points. Secondary outcomes were resource use, cost, and survival. Associations were estimated by regression modeling with adjustment for potential confounding. All adult patients having cardiac surgery between April 1, 1996, and December 31, 2003, with key exposure and outcome data were included (98%). Adjusted odds ratios for composite infection (737 of 8516) and ischemic outcomes (832 of 8518) for transfused versus nontransfused patients were 3.38 (95% confidence interval [CI], 2.60 to 4.40) and 3.35 (95% CI, 2.68 to 4.35), respectively. Transfusion was associated with increased relative cost of admission (any transfusion, 1.42 times [95% CI, 1.37 to 1.46], varying from 1.11 for 1 U to 3.35 for >9 U). At any time after their operations, transfused patients were less likely to have been discharged from hospital (hazard ratio [HR], 0.63; 95% CI, 0.60 to 0.67) and were more likely to have died (0 to 30 days: HR, 6.69; 95% CI, 3.66 to 15.1; 31 days to 1 year: HR, 2.59; 95% CI, 1.68 to 4.17; >1 year: HR, 1.32; 95% CI, 1.08 to 1.64).

Conclusions—Red blood cell transfusion in patients having cardiac surgery is strongly associated with both infection and ischemic postoperative morbidity, hospital stay, increased early and late mortality, and hospital costs. (***Circulation.* 2007;116:2544-2552.**)

Figure 4. Kaplan–Meier survival curve showing the cumulative proportion of patients who died over time according to whether patients had had an RBC transfusion.



Number at risk:

	0	1	2	3	4	5	6	7
Not transfused:	3689	3529	2925	2383	1842	1261	772	391
Transfused:	4909	4449	3913	3340	2773	2213	1713	1073

Gavin J. Murphy et al. Circulation. 2007;116:2544-2552

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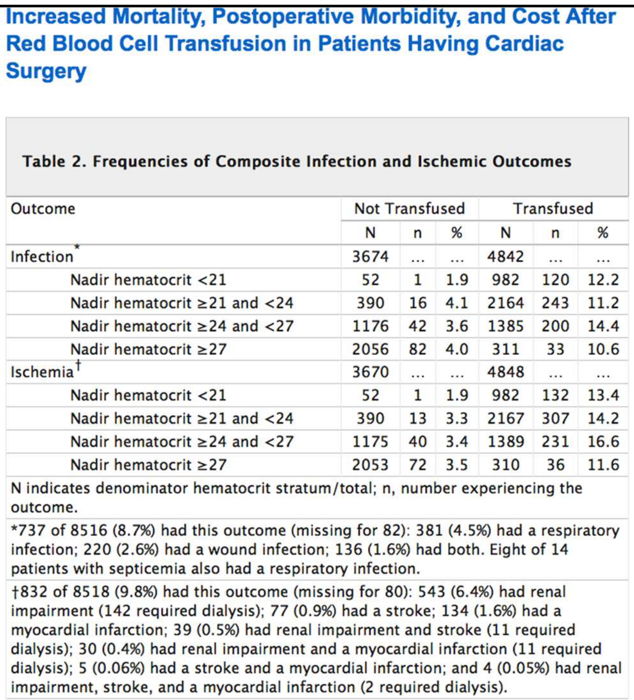


Increased Mortality, Postoperative Morbidity, and Cost After Red Blood Cell Transfusion in Patients Having Cardiac Surgery

Table 2. Frequencies of Composite Infection and Ischemic Outcomes

Outcome	Not Transfused			Transfused		
	N	n	%	N	n	%
Infection*	3674	…	…	4842	…	…
Nadir hematocrit <21	52	1	1.9	982	120	12.2
Nadir hematocrit ≥21 and <24	390	16	4.1	2164	243	11.2
Nadir hematocrit ≥24 and <27	1176	42	3.6	1385	200	14.4
Nadir hematocrit ≥27	2056	82	4.0	311	33	10.6
Ischemia†	3670	…	…	4848	…	…
Nadir hematocrit <21	52	1	1.9	982	132	13.4
Nadir hematocrit ≥21 and <24	390	13	3.3	2167	307	14.2
Nadir hematocrit ≥24 and <27	1175	40	3.4	1389	231	16.6
Nadir hematocrit ≥27	2053	72	3.5	310	36	11.6

N indicates denominator hematocrit stratum/total; n, number experiencing the outcome.

*737 of 8516 (8.7%) had this outcome (missing for 82): 381 (4.5%) had a respiratory infection; 220 (2.6%) had a wound infection; 136 (1.6%) had both. Eight of 14 patients with septicemia also had a respiratory infection.

†832 of 8518 (9.8%) had this outcome (missing for 80): 543 (6.4%) had renal impairment (142 required dialysis); 77 (0.9%) had a stroke; 134 (1.6%) had a myocardial infarction; 39 (0.5%) had renal impairment and stroke (11 required dialysis); 30 (0.4%) had renal impairment and a myocardial infarction (11 required dialysis); 5 (0.06%) had a stroke and a myocardial infarction; and 4 (0.05%) had renal impairment, stroke, and a myocardial infarction (2 required dialysis).

Transfusion of 1 and 2 Units of Red Blood Cells Is Associated With Increased Morbidity and Mortality

Presented at the Forty-ninth Annual Meeting of The Society of Thoracic Surgeons, Los Angeles, CA, Jan 26–30, 2013.

Gaetano Paone, MD, MHSA[a, ,], Donald S. Likosky, PhD[b], Robert Brewer, MD, MHSA[a], Patricia F. Theurer, BSN[c], Gail F. Bell, MSN[c], Chad M. Cogan, MS[d], Richard L. Prager, MD[e], for the Membership of the Michigan Society of Thoracic and Cardiovascular Surgeons

Background

This study examined the relationship between transfusion of 1 or 2 units of red blood cells (RBCs) and the risk of morbidity and mortality after isolated on-pump coronary artery bypass grafting (CABG).

Methods

A total of 22,785 consecutive patients underwent isolated on-pump CABG between January 1, 2008, and December 31, 2011 in Michigan. We excluded 5,950 patients who received three or more RBC units. Twenty-one preoperative variables significantly associated with transfusion by univariate analysis were included in a logistic regression model predicting transfusion, and propensity scores were calculated. Transfusion and the propensity score covariate were included in additional logistic regression models predicting mortality and each of 11 postoperative outcomes.

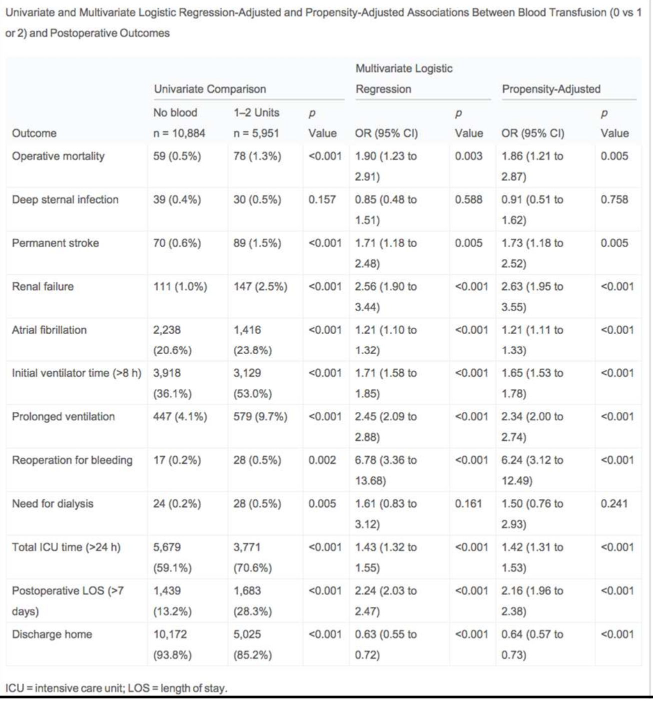
Results

Operative mortality for the study cohort of 16,835 patients was 0.8% overall, 0.5% for the 10,884 patients with no transfusion, and 1.3% for the 5,951 patients who received transfusion of 1 or 2 units (odds ratio 2.44; confidence interval 1.74 to 3.42; $p < 0.0001$). The association between transfusion and mortality lessened after propensity adjustment but remained highly significant (odds ratio 1.86; confidence interval 1.21 to 2.87; $p = 0.005$). Of the 11 postoperative outcomes studied, all but sternal wound infection and need for dialysis were also significantly associated with transfusion.

Conclusions

Transfusion of as little as 1 or 2 units of RBCs is common and is significantly associated with increased morbidity and mortality after on-pump CABG. The relationship persists after adjustment for preoperative risk factors. These results suggest that aggressive attempts at blood conservation and avoidance of even small amounts of RBC transfusion may improve outcomes after CABG.

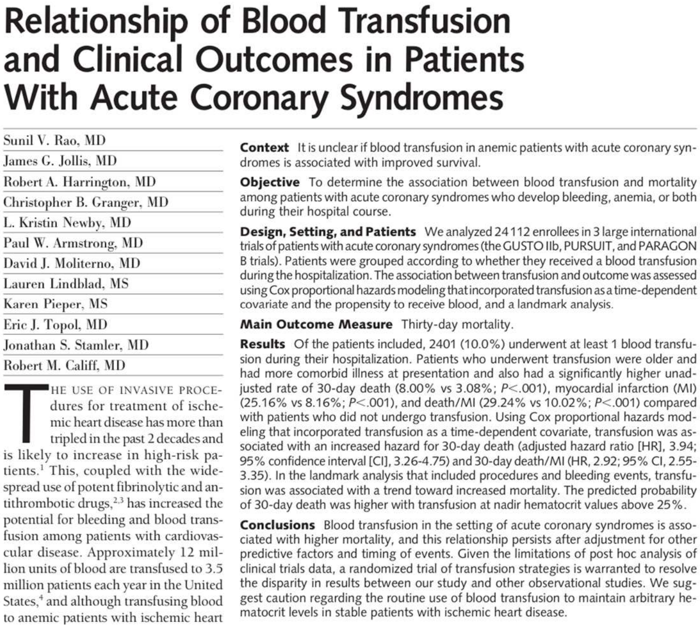
The Annals of Thoracic Surgery Volume 97, Issue 1, January 2014, Pages 87–94



Univariate and Multivariate Logistic Regression-Adjusted and Propensity-Adjusted Associations Between Blood Transfusion (0 vs 1 or 2) and Postoperative Outcomes

	Univariate Comparison			Multivariate Logistic Regression		Propensity-Adjusted	
Outcome	No blood n = 10,884	1–2 Units n = 5,951	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Operative mortality	59 (0.5%)	78 (1.3%)	<0.001	1.90 (1.23 to 2.91)	0.003	1.86 (1.21 to 2.87)	0.005
Deep sternal infection	39 (0.4%)	30 (0.5%)	0.157	0.85 (0.48 to 1.51)	0.588	0.91 (0.51 to 1.62)	0.758
Permanent stroke	70 (0.6%)	89 (1.5%)	<0.001	1.71 (1.18 to 2.48)	0.005	1.73 (1.18 to 2.52)	0.005
Renal failure	111 (1.0%)	147 (2.5%)	<0.001	2.56 (1.90 to 3.44)	<0.001	2.63 (1.95 to 3.55)	<0.001
Atrial fibrillation	2,238 (20.6%)	1,416 (23.8%)	<0.001	1.21 (1.10 to 1.32)	<0.001	1.21 (1.11 to 1.33)	<0.001
Initial ventilator time (>8 h)	3,918 (36.1%)	3,129 (53.0%)	<0.001	1.71 (1.58 to 1.85)	<0.001	1.65 (1.53 to 1.78)	<0.001
Prolonged ventilation	447 (4.1%)	579 (9.7%)	<0.001	2.45 (2.09 to 2.88)	<0.001	2.34 (2.00 to 2.74)	<0.001
Reoperation for bleeding	17 (0.2%)	28 (0.5%)	0.002	6.78 (3.36 to 13.68)	<0.001	6.24 (3.12 to 12.49)	<0.001
Need for dialysis	24 (0.2%)	28 (0.5%)	0.005	1.61 (0.83 to 3.12)	0.161	1.50 (0.76 to 2.93)	0.241
Total ICU time (>24 h)	5,679 (59.1%)	3,771 (70.6%)	<0.001	1.43 (1.32 to 1.55)	<0.001	1.42 (1.31 to 1.53)	<0.001
Postoperative LOS (>7 days)	1,439 (13.2%)	1,683 (28.3%)	<0.001	2.24 (2.03 to 2.47)	<0.001	2.16 (1.96 to 2.38)	<0.001
Discharge home	10,172 (93.8%)	5,025 (85.2%)	<0.001	0.63 (0.55 to 0.72)	<0.001	0.64 (0.57 to 0.73)	<0.001

ICU = intensive care unit; LOS = length of stay.



Relationship of Blood Transfusion and Clinical Outcomes in Patients With Acute Coronary Syndromes

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David J. Moliterno, MD
Lauren Lindblad, MS
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Context It is unclear if blood transfusion in anemic patients with acute coronary syndromes is associated with improved survival.

Objective To determine the association between blood transfusion and mortality among patients with acute coronary syndromes who develop bleeding, anemia, or both during their hospital course.

Design, Setting, and Patients We analyzed 24 112 enrollees in 3 large international trials of patients with acute coronary syndromes (the GUSTO IIb, PURSUIT, and PARAGON B trials). Patients were grouped according to whether they received a blood transfusion during the hospitalization. The association between transfusion and outcome was assessed using Cox proportional hazards modeling that incorporated transfusion as a time-dependent covariate and the propensity to receive blood, and a landmark analysis.

Main Outcome Measure Thirty-day mortality.

Results Of the patients included, 2401 (10.0%) underwent at least 1 blood transfusion during their hospitalization. Patients who underwent transfusion were older and had more comorbid illness at presentation and also had a significantly higher unadjusted rate of 30-day death (8.00% vs 3.08%; *P*<.001), myocardial infarction (MI) (25.16% vs 8.16%; *P*<.001), and death/MI (29.24% vs 10.02%; *P*<.001) compared with patients who did not undergo transfusion. Using Cox proportional hazards modeling that incorporated transfusion as a time-dependent covariate, transfusion was associated with an increased hazard for 30-day death (adjusted hazard ratio [HR], 3.94; 95% confidence interval [CI], 3.26-4.75) and 30-day death/MI (HR, 2.92; 95% CI, 2.55-3.35). In the landmark analysis that included procedures and bleeding events, transfusion was associated with a trend toward increased mortality. The predicted probability of 30-day death was higher with transfusion at nadir hematocrit values above 25%.

Conclusions Blood transfusion in the setting of acute coronary syndromes is associated with higher mortality, and this relationship persists after adjustment for other predictive factors and timing of events. Given the limitations of post hoc analysis of clinical trials data, a randomized trial of transfusion strategies is warranted to resolve the disparity in results between our study and other observational studies. We suggest caution regarding the routine use of blood transfusion to maintain arbitrary hematocrit levels in stable patients with ischemic heart disease.

THE USE OF INVASIVE PROCEDURES for treatment of ischemic heart disease has more than tripled in the past 2 decades and is likely to increase in high-risk patients.[1] This, coupled with the widespread use of potent fibrinolytic and antithrombotic drugs,[2,3] has increased the potential for bleeding and blood transfusion among patients with cardiovascular disease. Approximately 12 million units of blood are transfused to 3.5 million patients each year in the United States,[4] and although transfusing blood to anemic patients with ischemic heart

Rao, S. V. et al. JAMA 2004;292:1555-1562.

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Relationship of Blood Transfusion and Clinical Outcomes in Patients With Acute Coronary Syndromes

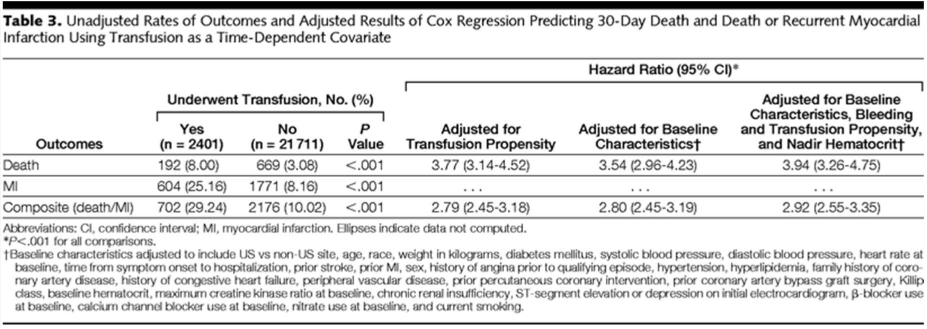

Table 3. Unadjusted Rates of Outcomes and Adjusted Results of Cox Regression Predicting 30-Day Death and Death or Recurrent Myocardial Infarction Using Transfusion as a Time-Dependent Covariate

	Underwent Transfusion, No. (%)			Hazard Ratio (95% CI)*		
Outcomes	Yes (n = 2401)	No (n = 21 711)	*P* Value	Adjusted for Transfusion Propensity	Adjusted for Baseline Characteristics†	Adjusted for Baseline Characteristics, Bleeding and Transfusion Propensity, and Nadir Hematocrit†
Death	192 (8.00)	669 (3.08)	<.001	3.77 (3.14-4.52)	3.54 (2.96-4.23)	3.94 (3.26-4.75)
MI	604 (25.16)	1771 (8.16)	<.001	. . .	. . .	. . .
Composite (death/MI)	702 (29.24)	2176 (10.02)	<.001	2.79 (2.45-3.18)	2.80 (2.45-3.19)	2.92 (2.55-3.35)

Abbreviations: CI, confidence interval; MI, myocardial infarction. Ellipses indicate data not computed.

*$P<.001$ for all comparisons.

†Baseline characteristics adjusted to include US vs non-US site, age, race, weight in kilograms, diabetes mellitus, systolic blood pressure, diastolic blood pressure, heart rate at baseline, time from symptom onset to hospitalization, prior stroke, prior MI, sex, history of angina prior to qualifying episode, hypertension, hyperlipidemia, family history of coronary artery disease, history of congestive heart failure, peripheral vascular disease, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, Killip class, baseline hematocrit, maximum creatine kinase ratio at baseline, chronic renal insufficiency, ST-segment elevation or depression on initial electrocardiogram, β-blocker use at baseline, calcium channel blocker use at baseline, nitrate use at baseline, and current smoking.

Rao, S. V. et al. JAMA 2004;292:1555-1562.

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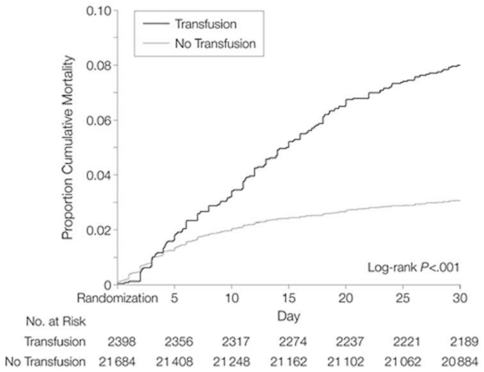
Kaplan-Meier Estimates of 30-Day Mortality Among Patients Who Did and Did Not Receive Blood Transfusion



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JAMA

Transfusion of stored, allogeneic RBCs does not appear to augment tissue oxygen delivery

- In sepsis studies, RBC transfusion is associated with increased calculated delivery but not consumption.
- Lactate and mucosal pH do not improve with transfusion.
- Transfusion is associated with an increase in ischemic complications.

Effect of Stored-Blood Transfusion on Oxygen Delivery in Patients With Sepsis

Paul E. Marik, MMed; William J. Sibbald, MD, FRCPC *JAMA.* 1993;269(23):3024-3029.
doi:10.1001/jama.1993.03500230106037.

ABSTRACT

Background. —Red blood cell transfusion is commonly used to augment systemic oxygen delivery to supranormal levels in patients with sepsis. However, clinical studies have not consistently demonstrated that this therapeutic maneuver is accompanied by an increase in oxygen utilization at either the whole-body level or within individual organs.

Study Objectives. —To determine the effect of red blood cell transfusion on gastrointestinal and whole-body oxygen uptake.

Design. —Prospective, controlled, interventional study.

Setting. —Multidisciplinary intensive care unit of a tertiary care teaching hospital.

Patients. —Twenty-three critically ill patients with sepsis undergoing mechanical ventilation.

Measurements and Main Results. —Systemic oxygen uptake was measured by indirect calorimetry and calculated by the Fick method. Gastric intramucosal pH as measured by tonometry was used to assess changes in splanchnic oxygen availability. Measurements were made prior to transfusion of 3 U of packed red blood cells. These were then repeated immediately following transfusion, as well as 3 and 6 hours later. There was no increase in systemic oxygen uptake measured by indirect calorimetry in any of the patients studied for up to 6 hours posttransfusion (including those patients with an elevated arterial lactate concentration). However, the calculated systemic oxygen uptake increased in parallel with the oxygen delivery in all the patients. More importantly, we found an inverse association between the change in gastric intramucosal pH and the age of the transfused blood (r=-.71; P<.001). In those patients receiving blood that had been stored for more than 15 days, the gastric intramucosal pH consistently decreased following the red blood cell transfusion.

Conclusion. —We failed to demonstrate a beneficial effect of red blood cell transfusion on measured systemic oxygen uptake in patients with sepsis. Patients receiving old transfused red blood cells developed evidence of splanchnic ischemia. We postulate that the poorly deformable transfused red blood cells cause microcirculatory occlusion in some organs, which may lead to tissue ischemia in some organs.(*JAMA.* 1993;269:3024-3029)

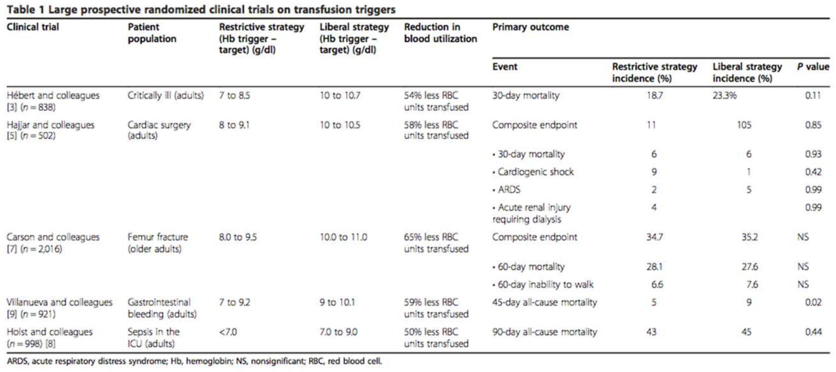
Possible mechanisms contributing to ischemic complications of RBC transfusions

- Decreased 2,3 DPG
- Decreased RBC deformability
- Increased NO scavenging
- Toxicity of catalytic iron

Kidney International 7 January 2015;
Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery
David E Leaf[1], Mohan Rajapurkar[2], Suhas S Lele[3], Banibrata Mukhopadhyay[2], James D Rawn[4], Gyorgy Frendl[5] and Sushrut S Waikar[1]

Catalytic iron, the chemical form of iron capable of participating in redox cycling, is a key mediator of acute kidney injury (AKI) in multiple animal models, but its role in human AKI has not been studied. Here we tested in a prospective cohort of 250 patients undergoing cardiac surgery whether plasma catalytic iron levels are elevated and associated with the composite outcome of AKI requiring renal replacement therapy or in-hospital mortality. Plasma catalytic iron, free hemoglobin, and other iron parameters were measured preoperatively, at the end of cardiopulmonary bypass, and on postoperative days 1 and 3. Plasma catalytic iron levels, but not other iron parameters, rose significantly at the end of cardiopulmonary bypass and were directly associated with bypass time and number of packed red blood cell transfusions. In multivariate analyses adjusting for age and preoperative eGFR, patients in the highest compared with the lowest quartile of catalytic iron on postoperative day 1 had a 6.71 greater odds of experiencing the primary outcome, and also had greater odds of AKI, hospital mortality, and postoperative myocardial injury. Thus, our data are consistent with and expand on findings from animal models demonstrating a pathologic role of catalytic iron in mediating adverse postoperative outcomes. Interventions aimed at reducing plasma catalytic iron levels as a strategy for preventing AKI in humans are warranted.

Prospective Randomized Trails



Mirski *et al. Critical Care* (2015) 19:202

Table 1 Large prospective randomized clinical trials on transfusion triggers

Clinical trial	Patient population	Restrictive strategy (Hb trigger – target) (g/dl)	Liberal strategy (Hb trigger – target) (g/dl)	Reduction in blood utilization	Primary outcome			
					Event	Restrictive strategy incidence (%)	Liberal strategy incidence (%)	*P* value
Hébert and colleagues [3] (*n* = 838)	Critically ill (adults)	7 to 8.5	10 to 10.7	54% less RBC units transfused	30-day mortality	18.7	23.3%	0.11
Hajjar and colleagues [5] (*n* = 502)	Cardiac surgery (adults)	8 to 9.1	10 to 10.5	58% less RBC units transfused	Composite endpoint	11	105	0.85
					• 30-day mortality	6	6	0.93
					• Cardiogenic shock	9	1	0.42
					• ARDS	2	5	0.99
					• Acute renal injury requiring dialysis	4		0.99
Carson and colleagues [7] (*n* = 2,016)	Femur fracture (older adults)	8.0 to 9.5	10.0 to 11.0	65% less RBC units transfused	Composite endpoint	34.7	35.2	NS
					• 60-day mortality	28.1	27.6	NS
					• 60-day inability to walk	6.6	7.6	NS
Villanueva and colleagues [9] (*n* = 921)	Gastrointestinal bleeding (adults)	7 to 9.2	9 to 10.1	59% less RBC units transfused	45-day all-cause mortality	5	9	0.02
Holst and colleagues (*n* = 998) [8]	Sepsis in the ICU (adults)	<7.0	7.0 to 9.0	50% less RBC units transfused	90-day all-cause mortality	43	45	0.44

ARDS, acute respiratory distress syndrome; Hb, hemoglobin; NS, nonsignificant; RBC, red blood cell.

Health Care–Associated Infection After Red Blood Cell Transfusion A Systematic Review and Meta-analysis

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JAMA. 2014;311(13):1317-1326

Importance The association between red blood cell (RBC) transfusion strategies and health care–associated infection is not fully understood.

Objective To evaluate whether RBC transfusion thresholds are associated with the risk of infection and whether risk is independent of leukocyte reduction.

Data Sources MEDLINE, EMBASE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, Cochrane Database of Sytematic Reviews, ClinicalTrials.gov, International Clinical Trials Registry, and the International Standard Randomized Controlled Trial Number register were searched through January 22, 2014.

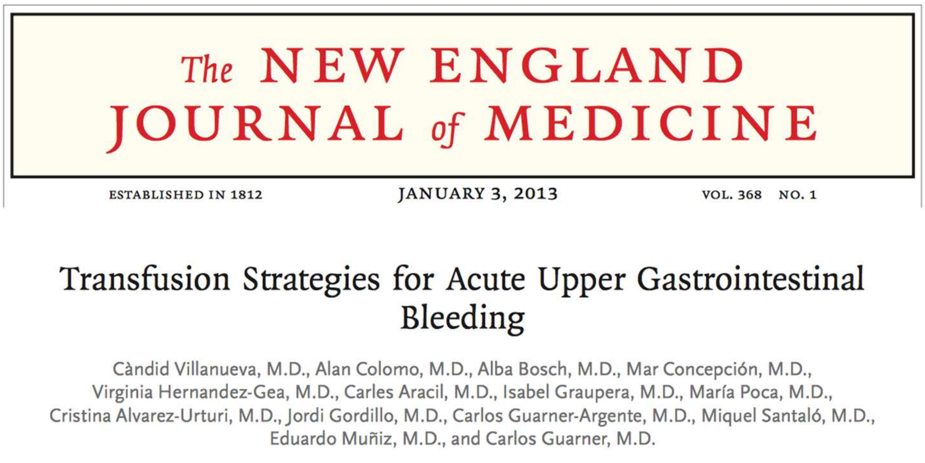
Study Selection Randomized clinical trials with restrictive vs liberal RBC transfusion strategies.

Data Extraction and Synthesis Twenty randomized trials with 8598 patients met eligibility criteria, of which 17 trials (n = 7456 patients) contained sufficient information for meta-analyses. DerSimonian and Laird random-effects models were used to report pooled risk ratios. Absolute risks of infection were calculated using the profile likelihood random-effects method.

Main Outcomes and Measures Incidence of health care–associated infection such as pneumonia, mediastinitis, wound infection, and sepsis.

Results The pooled risk of all serious infections was 10.6% (95% CI, 5.6%-15.9%) in the restrictive group and 12.7% (95% CI, 7.0%-18.7%) in the liberal group. The risk ratio (RR) for the association between transfusion strategies and infection (serious infections and selected infections, combined) was 0.92 (95% CI, 0.82-1.04) with little heterogeneity ($I2$ = 6.3%; τ2 = .0041). The RR for the association between transfusion strategies and serious infection was 0.84 (95% CI, 0.73-0.96; $I2$ = 0%, τ2 <.0001). The number needed to treat (NNT) with restrictive strategies to prevent serious infection was 48 (95% CI, 36-71). The risk of infection remained reduced with a restrictive strategy, even with leukocyte reduction (RR, 0.83 [95% CI, 0.69-0.99]). For trials with a restrictive hemoglobin threshold of <7.0 g/dL, the RR was 0.86 (95% CI, 0.72-1.02). With stratification by patient type, the RR for serious infection was 0.72 (95% CI, 0.53-0.97) in patients undergoing orthopedic surgery and 0.51 (95% CI, 0.28-0.95) in patients presenting with sepsis. There were no significant differences in the incidence of infection by RBC threshold for patients with cardiac disease, the critically ill, those with acute upper gastrointestinal bleeding, or for infants with low birth weight.

Conclusions and Relevance Among hospitalized patients, a restrictive RBC transfusion strategy compared with a liberal transfusion strategy was not associated with a reduced risk of health care–associated infection overall, although it was associated with a reduced risk of serious infection. Implementing restrictive strategies may have the potential to lower the incidence of serious health care–associated infection.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2013 VOL. 368 NO. 1

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

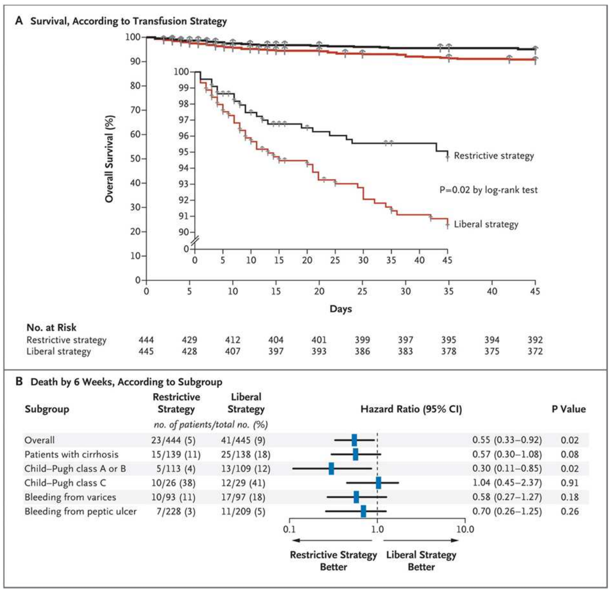
Càndid Villanueva, M.D., Alan Colomo, M.D., Alba Bosch, M.D., Mar Concepción, M.D., Virginia Hernandez-Gea, M.D., Carles Aracil, M.D., Isabel Graupera, M.D., María Poca, M.D., Cristina Alvarez-Urturi, M.D., Jordi Gordillo, M.D., Carlos Guarner-Argente, M.D., Miquel Santaló, M.D., Eduardo Muñiz, M.D., and Carlos Guarner, M.D.

BACKGROUND
The hemoglobin threshold for transfusion of red cells in patients with acute gastrointestinal bleeding is controversial. We compared the efficacy and safety of a restrictive transfusion strategy with those of a liberal transfusion strategy.
Full Text of Background...

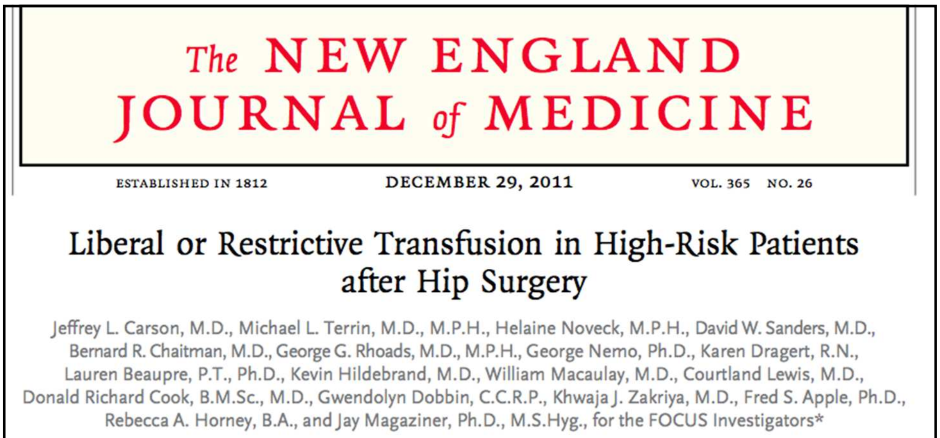
METHODS
We enrolled 921 patients with severe acute upper gastrointestinal bleeding and randomly assigned 461 of them to a restrictive strategy (transfusion when the hemoglobin level fell below 7 g per deciliter) and 460 to a liberal strategy (transfusion when the hemoglobin fell below 9 g per deciliter). Randomization was stratified according to the presence or absence of liver cirrhosis.
Full Text of Methods...

RESULTS
A total of 225 patients assigned to the restrictive strategy (51%), as compared with 61 assigned to the liberal strategy (14%), did not receive transfusions (P<0.001). The probability of survival at 6 weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95% vs. 91%; hazard ratio for death with restrictive strategy, 0.55; 95% confidence interval [CI], 0.33 to 0.92; P=0.02). Further bleeding occurred in 10% of the patients in the restrictive-strategy group as compared with 16% of the patients in the liberal-strategy group (P=0.01), and adverse events occurred in 40% as compared with 48% (P=0.02). The probability of survival was slightly higher with the restrictive strategy than with the liberal strategy in the subgroup of patients who had bleeding associated with a peptic ulcer (hazard ratio, 0.70; 95% CI, 0.26 to 1.25) and was significantly higher in the subgroup of patients with cirrhosis and Child–Pugh class A or B disease (hazard ratio, 0.30; 95% CI, 0.11 to 0.85), but not in those with cirrhosis and Child–Pugh class C disease (hazard ratio, 1.04; 95% CI, 0.45 to 2.37). Within the first 5 days, the portal-pressure gradient increased significantly in patients assigned to the liberal strategy (P=0.03) but not in those assigned to the restrictive strategy.
Full Text of Results...

CONCLUSIONS
As compared with a liberal transfusion strategy, a restrictive strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding.



Villanueva C et al. N Engl J Med 2013;368:11-21.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 29, 2011 VOL. 365 NO. 26

Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery

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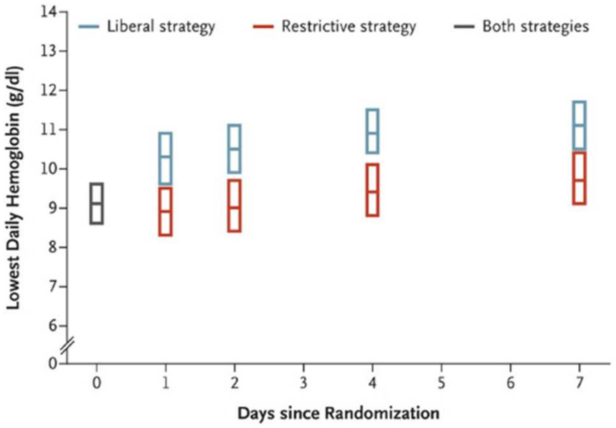
2000 orthopedic surgery patients.
Transfusion thresholds: Hgb10 mg/dl vs 8 mg/dl.
No statistically significant differences in outcomes including survival and ability to walk independently.



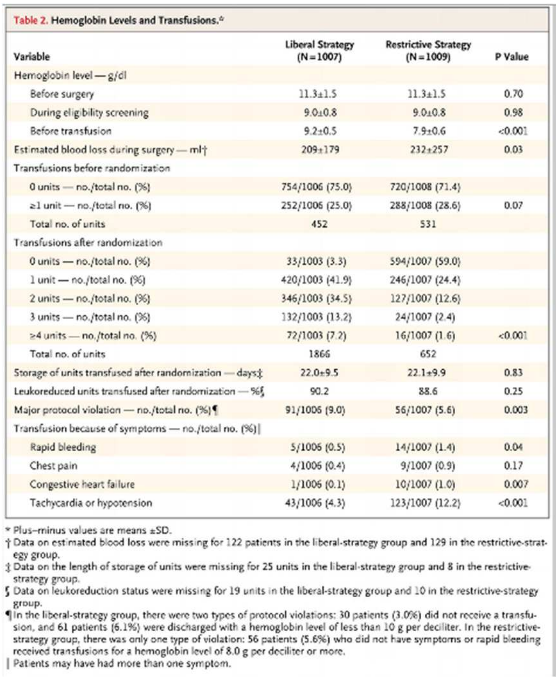


Table 2. Hemoglobin Levels and Transfusions.[*]

Variable	Liberal Strategy (N=1007)	Restrictive Strategy (N=1009)	P Value
Hemoglobin level — g/dl			
Before surgery	11.3±1.5	11.3±1.5	0.70
During eligibility screening	9.0±0.8	9.0±0.8	0.98
Before transfusion	9.2±0.5	7.9±0.6	<0.001
Estimated blood loss during surgery — ml[†]	209±179	232±257	0.03
Transfusions before randomization			
0 units — no./total no. (%)	754/1006 (75.0)	720/1008 (71.4)	
≥1 unit — no./total no. (%)	252/1006 (25.0)	288/1008 (28.6)	0.07
Total no. of units	452	531	
Transfusions after randomization			
0 units — no./total no. (%)	33/1003 (3.3)	594/1007 (59.0)	
1 unit — no./total no. (%)	420/1003 (41.9)	246/1007 (24.4)	
2 units — no./total no. (%)	346/1003 (34.5)	127/1007 (12.6)	
3 units — no./total no. (%)	132/1003 (13.2)	24/1007 (2.4)	
≥4 units — no./total no. (%)	72/1003 (7.2)	16/1007 (1.6)	<0.001
Total no. of units	1866	652	
Storage of units transfused after randomization — days[‡]	22.0±9.5	22.1±9.9	0.83
Leukoreduced units transfused after randomization — %[§]	90.2	88.6	0.25
Major protocol violation — no./total no. (%)[¶]	91/1006 (9.0)	56/1007 (5.6)	0.003
Transfusion because of symptoms — no./total no. (%)[‖]			
Rapid bleeding	5/1006 (0.5)	14/1007 (1.4)	0.04
Chest pain	4/1006 (0.4)	9/1007 (0.9)	0.17
Congestive heart failure	1/1006 (0.1)	10/1007 (1.0)	0.007
Tachycardia or hypotension	43/1006 (4.3)	123/1007 (12.2)	<0.001

[*] Plus–minus values are means ±SD.

[†] Data on estimated blood loss were missing for 122 patients in the liberal-strategy group and 129 in the restrictive-strategy group.

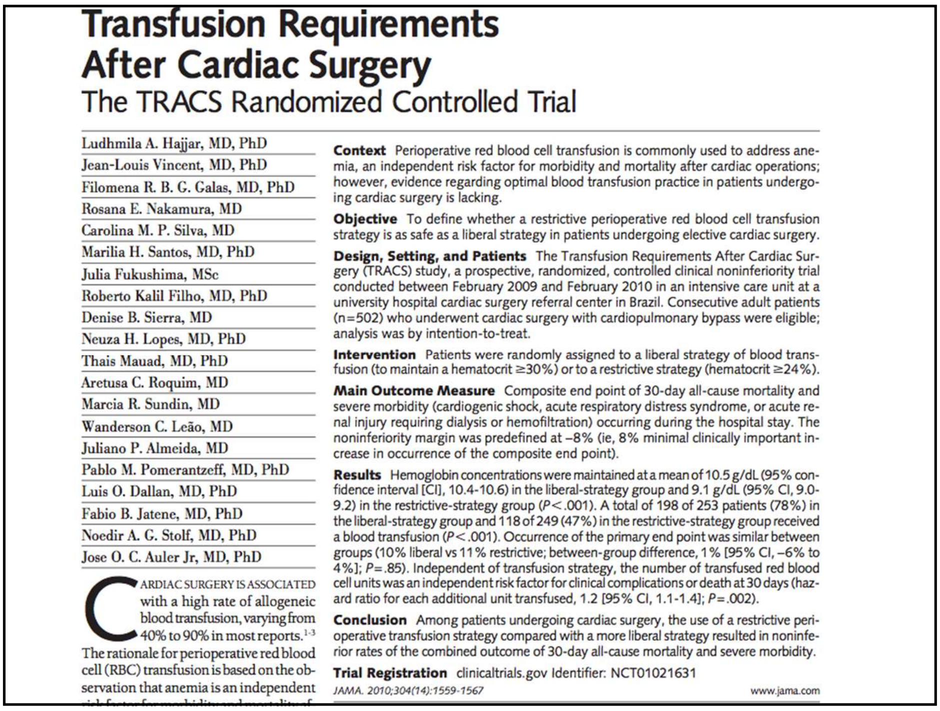
[‡] Data on the length of storage of units were missing for 25 units in the liberal-strategy group and 8 in the restrictive-strategy group.

[§] Data on leukoreduction status were missing for 19 units in the liberal-strategy group and 10 in the restrictive-strategy group.

[¶] In the liberal-strategy group, there were two types of protocol violations: 30 patients (3.0%) did not receive a transfusion, and 61 patients (6.1%) were discharged with a hemoglobin level of less than 10 g per deciliter. In the restrictive-strategy group, there was only one type of violation: 56 patients (5.6%) who did not have symptoms or rapid bleeding received transfusions for a hemoglobin level of 8.0 g per deciliter or more.

[‖] Patients may have had more than one symptom.

Trials which evaluate restrictive versus liberal transfusion strategies address the risks and benefits of transfusion indirectly. Outcomes appear to differ more when adjusted for number of blood transfusions than for transfusion strategy.



Transfusion Requirements After Cardiac Surgery

The TRACS Randomized Controlled Trial

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Jose O. C. Auler Jr, MD, PhD

Context Perioperative red blood cell transfusion is commonly used to address anemia, an independent risk factor for morbidity and mortality after cardiac operations; however, evidence regarding optimal blood transfusion practice in patients undergoing cardiac surgery is lacking.

Objective To define whether a restrictive perioperative red blood cell transfusion strategy is as safe as a liberal strategy in patients undergoing elective cardiac surgery.

Design, Setting, and Patients The Transfusion Requirements After Cardiac Surgery (TRACS) study, a prospective, randomized, controlled clinical noninferiority trial conducted between February 2009 and February 2010 in an intensive care unit at a university hospital cardiac surgery referral center in Brazil. Consecutive adult patients (n=502) who underwent cardiac surgery with cardiopulmonary bypass were eligible; analysis was by intention-to-treat.

Intervention Patients were randomly assigned to a liberal strategy of blood transfusion (to maintain a hematocrit ≥30%) or to a restrictive strategy (hematocrit ≥24%).

Main Outcome Measure Composite end point of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration) occurring during the hospital stay. The noninferiority margin was predefined at –8% (ie, 8% minimal clinically important increase in occurrence of the composite end point).

Results Hemoglobin concentrations were maintained at a mean of 10.5 g/dL (95% confidence interval [CI], 10.4-10.6) in the liberal-strategy group and 9.1 g/dL (95% CI, 9.0-9.2) in the restrictive-strategy group ($P<.001$). A total of 198 of 253 patients (78%) in the liberal-strategy group and 118 of 249 (47%) in the restrictive-strategy group received a blood transfusion ($P<.001$). Occurrence of the primary end point was similar between groups (10% liberal vs 11% restrictive; between-group difference, 1% [95% CI, –6% to 4%]; $P=.85$). Independent of transfusion strategy, the number of transfused red blood cell units was an independent risk factor for clinical complications or death at 30 days (hazard ratio for each additional unit transfused, 1.2 [95% CI, 1.1-1.4]; $P=.002$).

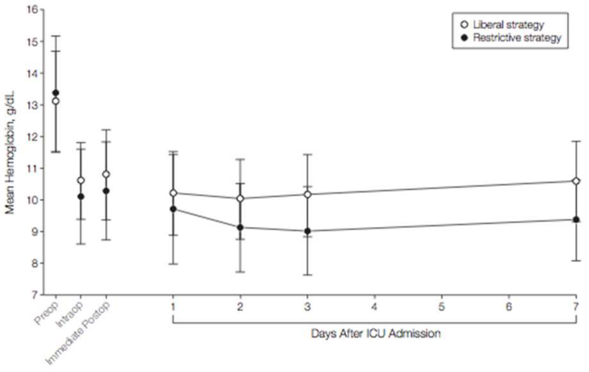
Conclusion Among patients undergoing cardiac surgery, the use of a restrictive perioperative transfusion strategy compared with a more liberal strategy resulted in noninferior rates of the combined outcome of 30-day all-cause mortality and severe morbidity.

Trial Registration clinicaltrials.gov Identifier: NCT01021631

JAMA. 2010;304(14):1559-1567 www.jama.com

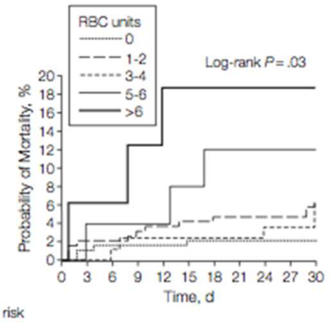
CARDIAC SURGERY IS ASSOCIATED with a high rate of allogeneic blood transfusion, varying from 40% to 90% in most reports.[1-3] The rationale for perioperative red blood cell (RBC) transfusion is based on the observation that anemia is an independent

Figure 2. Mean Hemoglobin Levels During the Study According to Transfusion Strategy



$P<.05$ between the groups at all points following preop. Error bars indicate 95% confidence intervals. ICU indicates intensive care unit.

Figure 4. Kaplan-Meier Estimates of 30-Day Survival Based on Number of Red Blood Cell (RBC) Units Transfused



No. at risk RBC units						
0	186	184	183	182	182	181
1-2	191	187	184	182	182	179
3-4	84	83	82	82	81	80
5-6	25	24	24	22	22	21
>6	16	15	13	13	13	12

Time zero was just after randomization (12 hours before surgery). With 0 RBC units as the reference category, the hazard ratio was 2.97 (95% confidence interval [CI], 0.96-9.21) ($P = .06$) for 1 to 2 RBC units; 2.78 (95% CI, 0.75-10.35) ($P = .13$) for 3 to 4 units; 5.82 (95% CI, 1.30-26.02) ($P = .02$) for 5 to 6 units; and 9.70 (95% CI, 2.17-43.34) ($P = .003$) for more than 6 units.

The NEW ENGLAND JOURNAL of MEDICINE

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Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

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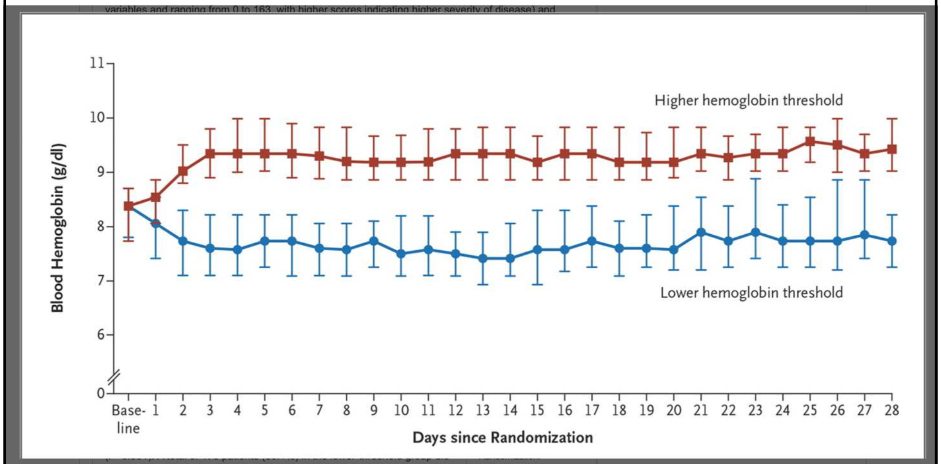


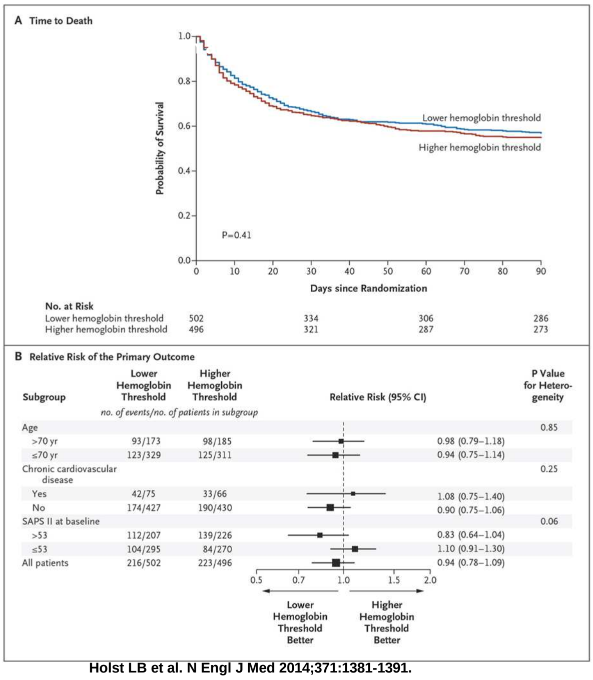
Figure 2

Blood Hemoglobin Levels in Patients in the ICU at Baseline and after Randomization.

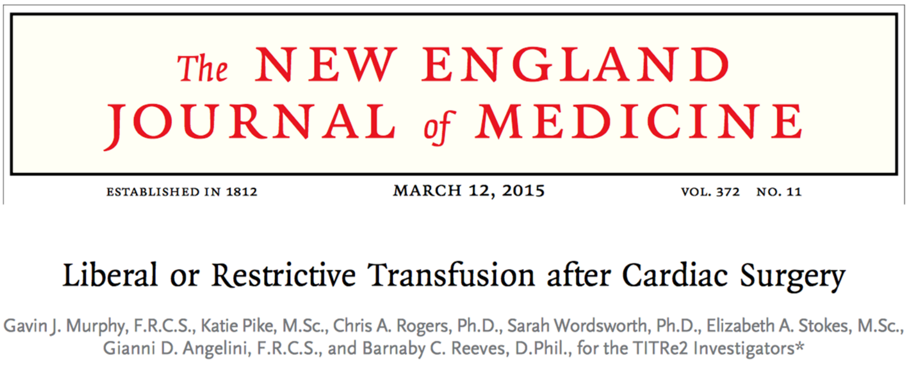
The graphs show the median daily lowest levels of blood hemoglobin in the lower-threshold group and the higher-threshold group. Baseline values were the lowest blood hemoglobin level measured in the 24 hours before randomization. Day 1 was defined as the time of randomization to the end of that day and lasted a median of 15 hours in the lower-threshold group and 14 hours in the higher-threshold group. The I bars indicate the 25th and 75th percentiles.

Table S5. Number of patients stratified by the number of units transfused

	Lower Hb-threshold (N=488)	Higher Hb-threshold (N=489)
	no./total no. (%)	
0 units	176/488 (36)	6/489 (1)
1 unit	88/488 (18)	70/489 (14)
2 units	57/488 (12)	85/489 (17)
3 units	47/488 (10)	80/489 (16)
4 units	27/488 (6)	53/489 (11)
5 or more units	93/488 (19)	195/489 (40)



Holst LB et al. N Engl J Med 2014;371:1381-1391.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 12, 2015 VOL. 372 NO. 11

Liberal or Restrictive Transfusion after Cardiac Surgery

Gavin J. Murphy, F.R.C.S., Katie Pike, M.Sc., Chris A. Rogers, Ph.D., Sarah Wordsworth, Ph.D., Elizabeth A. Stokes, M.Sc., Gianni D. Angelini, F.R.C.S., and Barnaby C. Reeves, D.Phil., for the TITRe2 Investigators*

Liberal or Restrictive Transfusion after Cardiac Surgery

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N Engl J Med 2015; 372:997

BACKGROUND
Whether a restrictive threshold for hemoglobin level in red-cell transfusions, as compared with a liberal threshold, reduces postoperative morbidity and health care costs after cardiac surgery is uncertain.

METHODS
We conducted a multicenter, parallel-group trial in which patients older than 16 years of age who were undergoing nonemergency cardiac surgery were recruited from 17 centers in the United Kingdom. Patients with a postoperative hemoglobin level of less than 9 g per deciliter were randomly assigned to a restrictive transfusion threshold (hemoglobin level <7.5 g per deciliter) or a liberal transfusion threshold (hemoglobin level <9 g per deciliter). The primary outcome was a serious infection (sepsis or wound infection) or an ischemic event (permanent stroke [confirmation on brain imaging and deficit in motor, sensory, or coordination functions], myocardial infarction, infarction of the gut, or acute kidney injury) within 3 months after randomization. Health care costs, excluding the index surgery, were estimated from the day of surgery to 3 months after surgery.

RESULTS
A total of 2007 patients underwent randomization; 4 participants withdrew, leaving 1000 in the restrictive-threshold group and 1003 in the liberal-threshold group. Transfusion rates after randomization were 53.4% and 92.2% in the two groups, respectively. The primary outcome occurred in 35.1% of the patients in the restrictive-threshold group and 33.0% of the patients in the liberal-threshold group (odds ratio, 1.11; 95% confidence interval [CI], 0.91 to 1.34; P=0.30); there was no indication of heterogeneity according to subgroup. There were more deaths in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; P=0.045). Serious postoperative complications, excluding primary-outcome events, occurred in 35.7% of participants in the restrictive-threshold group and 34.2% of participants in the liberal-threshold group. Total costs did not differ significantly between the groups.

CONCLUSIONS
A restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity or health care costs.

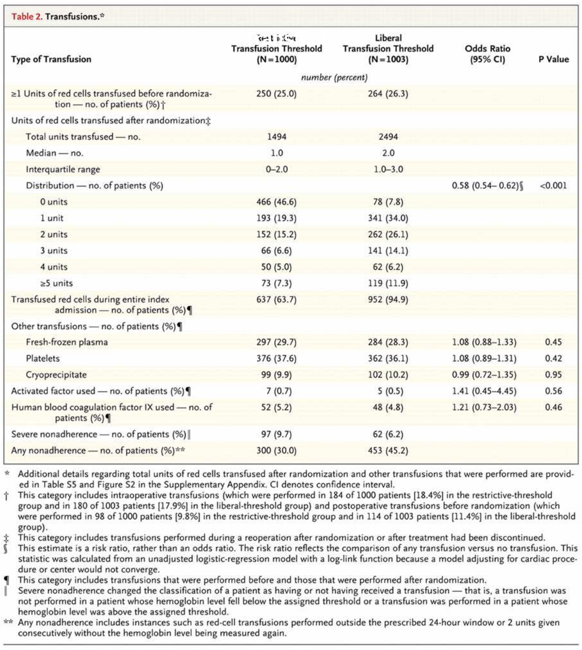


Table 2. Transfusions.*

Type of Transfusion	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)	Odds Ratio (95% CI)	P Value
	number (percent)			
≥1 Units of red cells transfused before randomization — no. of patients (%)†	250 (25.0)	264 (26.3)		
Units of red cells transfused after randomization‡				
Total units transfused — no.	1494	2494		
Median — no.	1.0	2.0		
Interquartile range	0–2.0	1.0–3.0		
Distribution — no. of patients (%)			0.58 (0.54– 0.62)§	<0.001
0 units	466 (46.6)	78 (7.8)		
1 unit	193 (19.3)	341 (34.0)		
2 units	152 (15.2)	262 (26.1)		
3 units	66 (6.6)	141 (14.1)		
4 units	50 (5.0)	62 (6.2)		
≥5 units	73 (7.3)	119 (11.9)		
Transfused red cells during entire index admission — no. of patients (%)¶	637 (63.7)	952 (94.9)		
Other transfusions — no. of patients (%)¶				
Fresh-frozen plasma	297 (29.7)	284 (28.3)	1.08 (0.88–1.33)	0.45
Platelets	376 (37.6)	362 (36.1)	1.08 (0.89–1.31)	0.42
Cryoprecipitate	99 (9.9)	102 (10.2)	0.99 (0.72–1.35)	0.95
Activated factor used — no. of patients (%)¶	7 (0.7)	5 (0.5)	1.41 (0.45–4.45)	0.56
Human blood coagulation factor IX used — no. of patients (%)¶	52 (5.2)	48 (4.8)	1.21 (0.73–2.03)	0.46
Severe nonadherence — no. of patients (%)‖	97 (9.7)	62 (6.2)		
Any nonadherence — no. of patients (%)**	300 (30.0)	453 (45.2)		

* Additional details regarding total units of red cells transfused after randomization and other transfusions that were performed are provided in Table S5 and Figure S2 in the Supplementary Appendix. CI denotes confidence interval.

† This category includes intraoperative transfusions (which were performed in 184 of 1000 patients [18.4%] in the restrictive-threshold group and in 180 of 1003 patients [17.9%] in the liberal-threshold group) and postoperative transfusions before randomization (which were performed in 98 of 1000 patients [9.8%] in the restrictive-threshold group and in 114 of 1003 patients [11.4%] in the liberal-threshold group).

‡ This category includes transfusions performed during a reoperation after randomization or after treatment had been discontinued.

§ This estimate is a risk ratio, rather than an odds ratio. The risk ratio reflects the comparison of any transfusion versus no transfusion. This statistic was calculated from an unadjusted logistic-regression model with a log-link function because a model adjusting for cardiac procedure or center would not converge.

¶ This category includes transfusions that were performed before and those that were performed after randomization.

‖ Severe nonadherence changed the classification of a patient as having or not having received a transfusion — that is, a transfusion was not performed in a patient whose hemoglobin level fell below the assigned threshold or a transfusion was performed in a patient whose hemoglobin level was above the assigned threshold.

** Any nonadherence includes instances such as red-cell transfusions performed outside the prescribed 24-hour window or 2 units given consecutively without the hemoglobin level being measured again.

Murphy GJ et al. N Engl J Med 2015;372:997-1008.

Guidelines

Clinical Practice Guidelines From the AABB Red Blood Cell Transfusion Thresholds and Storage

Jeffrey L. Carson, MD; Gordon Guyatt, MD; Nancy M. Heddle, MSc; et al JAMA. 2016;316(19):2025-203

Clinical Practice Guidelines From the AABB 2016

- These guidelines are based on randomized controlled trials which show that restrictive strategies and liberal strategies result, for the most part, in comparable outcomes.

- The AABB recommends using a restrictive hemoglobin transfusion threshold of 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, but a hemoglobin transfusion threshold of 8 g/dL for patients undergoing orthopedic or cardiac surgery and for those with underlying cardiovascular disease. The reason for the different thresholds is that the RCTs performed in the later groups of patients used a hemoglobin transfusion threshold of 8 g/dL and not a threshold of 7 g/dL.

Clinical Practice Guidelines From the AABB 2016

- The committee chose not to recommend for or against a liberal or restrictive transfusion threshold in patients with acute coronary syndrome.
- There is no evidence from randomized controlled trials that increasing age of stored blood has an effect on outcomes.
- Standard practice should be to initiate a transfusion with 1 unit of blood rather than 2 units.

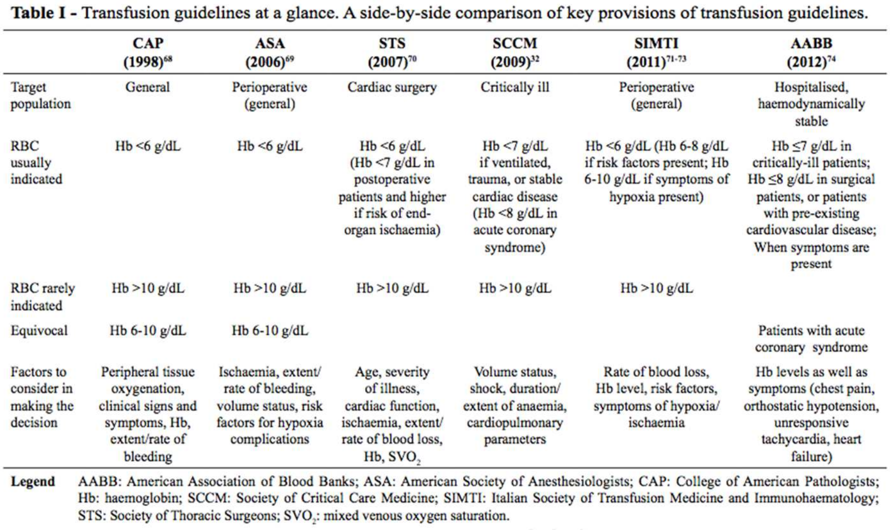
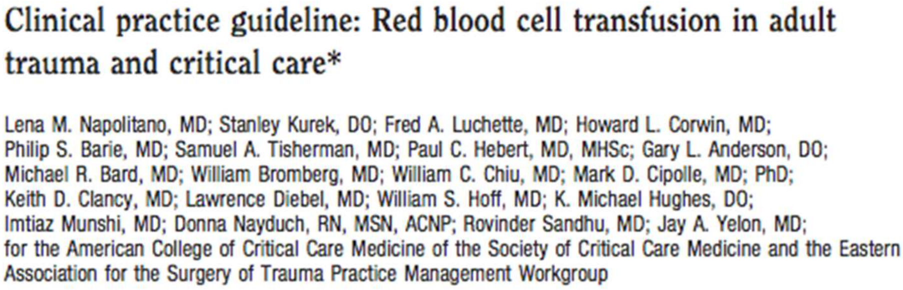


Table I - Transfusion guidelines at a glance. A side-by-side comparison of key provisions of transfusion guidelines.

	CAP (1998)[68]	**ASA (2006)**[69]	**STS (2007)**[70]	**SCCM (2009)**[32]	**SIMTI (2011)**[71-73]	**AABB (2012)**[74]
Target population	General	Perioperative (general)	Cardiac surgery	Critically ill	Perioperative (general)	Hospitalised, haemodynamically stable
RBC usually indicated	Hb <6 g/dL	Hb <6 g/dL	Hb <6 g/dL (Hb <7 g/dL in postoperative patients and higher if risk of end-organ ischaemia)	Hb <7 g/dL if ventilated, trauma, or stable cardiac disease (Hb <8 g/dL in acute coronary syndrome)	Hb <6 g/dL (Hb 6-8 g/dL if risk factors present; Hb 6-10 g/dL if symptoms of hypoxia present)	Hb ≤7 g/dL in critically-ill patients; Hb ≤8 g/dL in surgical patients, or patients with pre-existing cardiovascular disease; When symptoms are present
RBC rarely indicated	Hb >10 g/dL	Hb >10 g/dL	Hb >10 g/dL	Hb >10 g/dL	Hb >10 g/dL	
Equivocal	Hb 6-10 g/dL	Hb 6-10 g/dL				Patients with acute coronary syndrome
Factors to consider in making the decision	Peripheral tissue oxygenation, clinical signs and symptoms, Hb, extent/rate of bleeding	Ischaemia, extent/ rate of bleeding, volume status, risk factors for hypoxia complications	Age, severity of illness, cardiac function, ischaemia, extent/ rate of blood loss, Hb, SVO_2	Volume status, shock, duration/ extent of anaemia, cardiopulmonary parameters	Rate of blood loss, Hb level, risk factors, symptoms of hypoxia/ ischaemia	Hb levels as well as symptoms (chest pain, orthostatic hypotension, unresponsive tachycardia, heart failure)

Legend AABB: American Association of Blood Banks; ASA: American Society of Anesthesiologists; CAP: College of American Pathologists; Hb: haemoglobin; SCCM: Society of Critical Care Medicine; SIMTI: Italian Society of Transfusion Medicine and Immunohaematology; STS: Society of Thoracic Surgeons; SVO_2: mixed venous oxygen saturation.

Shander et al, A New Perspective on Best Transfusion Practices, Blood Transfus DOI 10.245



Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care*

Lena M. Napolitano, MD; Stanley Kurek, DO; Fred A. Luchette, MD; Howard L. Corwin, MD;
Philip S. Barie, MD; Samuel A. Tisherman, MD; Paul C. Hebert, MD, MHSc; Gary L. Anderson, DO;
Michael R. Bard, MD; William Bromberg, MD; William C. Chiu, MD; Mark D. Cipolle, MD; PhD;
Keith D. Clancy, MD; Lawrence Diebel, MD; William S. Hoff, MD; K. Michael Hughes, DO;
Imtiaz Munshi, MD; Donna Nayduch, RN, MSN, ACNP; Rovinder Sandhu, MD; Jay A. Yelon, MD;
for the American College of Critical Care Medicine of the Society of Critical Care Medicine and the Eastern Association for the Surgery of Trauma Practice Management Workgroup

Critical Care Medicine 2009; 37:3124 - 3157

Critical Care Clinical Practice Guidelines: Risks of Transfusion

- RBC transfusion is independently associated with nosocomial wound infection, pneumonia and sepsis.
- RBC transfusion is independently associated with multisystem organ failure and systemic inflammatory response syndrome.
- RBC transfusion is independently associated with acute lung injury and ARDS.
- RBC transfusion is independently associated with increased ICU and hospital length of stay, increased complications and increased mortality.

Critical Care Clinical Practice Guidelines

- Restrictive strategies (transfuse can be considered when Hb < 7 g/dl) are favored for stable, nonbleeding patients, including those with coronary disease, mechanical ventilation requirements and neurologic injury.

- In sepsis, there is no evidence that transfusion improves oxygen delivery.

Critical Care Clinical Practice Guidelines

- Two units should not routinely be transfused when transfusion is indicated.
- Patients with active coronary disease may benefit when transfused for a Hb < 8 g/dL.

- Blood products should be given for a clinical indication, not to treat a number

A. Recommendations Regarding Indications for RBC Transfusion in the General Critically Ill Patient

- RBC transfusion is indicated for patients with evidence of hemorrhagic shock. (Level 1)
- RBC transfusion may be indicated for patients with evidence of acute hemorrhage and hemodynamic instability or inadequate oxygen delivery. (Level 1)
- A “restrictive” strategy of RBC transfusion (transfuse when Hb <7 g/dL) is as effective as a “liberal” transfusion strategy (transfusion when Hb <10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia. (Level 1)
- The use of only Hb level as a “trigger” for transfusion should be avoided. Decision for RBC transfusion should be based on an individual patient’ sintravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters. (Level 2)
- In the absence of acute hemorrhage RBC, transfusion should be given as single units. (Level 2)
- Consider transfusion if Hb <7 g/dL in critically ill patients requiring mechanical ventilation (MV). There is no benefit of a “liberal”transfusion strategy (transfusion when Hb <10 g/dL) in critically ill patients requiring MV. (Level 2)

7. Consider transfusion if Hb <7 g/dL in resuscitated critically ill trauma patients. There is no benefit of a “liberal” transfusion strategy (transfusion when Hb <10 g/dL) in resuscitated critically ill trauma patients. (Level 2)
8. Consider transfusion if Hb <7 g/dL in critically ill patients with stable cardiac disease. There is no benefit of a “liberal” transfusion strategy(transfusion when Hb <10 g/dL) in critically ill patients with stable cardiac disease. (Level 2)
9. RBC transfusion should not be considered as an absolute method to improve tissue oxygen consumption in critically ill patients. (Level 2)
10. RBC transfusion may be beneficial in patients with acute coronary syndromes (ACS) who are anemic (Hb < 8 g/dL) on hospital admission. (Level 3)

Strategies for Minimizing Blood Transfusion

- Fewer blood draws
- Attention to surgical technique
- Adherence to guidelines both in and outside of the ICU
- Treat everyone like a Jehovah’s witness

Outcome of Patients Who Refuse Transfusion After Cardiac Surgery
A Natural Experiment With Severe Blood Conservation
Gregory Pattakos, MD, MS; Colleen G. Koch, MD, MS, MBA; Mariano E. Brizzio, MD; Lillian H. Batizy, MS; Joseph F. Sabik III, MD; Eugene H. Blackstone, MD; Michael S. Lauer, MD
Arch Intern Med. 2012;172(15):1154-1160.

- **Background** Jehovah's Witness patients (Witnesses) who undergo cardiac surgery provide a unique natural experiment in severe blood conservation because anemia, transfusion, erythropoietin, and antifibrinolytics have attendant risks. Our objective was to compare morbidity and long-term survival of Witnesses undergoing cardiac surgery with a similarly matched group of patients who received transfusions.
- **Methods** A total of 322 Witnesses and 87 453 non-Witnesses underwent cardiac surgery at our center from January 1, 1983, to January 1, 2011. All Witnesses prospectively refused blood transfusions. Among non-Witnesses, 38 467 did not receive blood transfusions and 48 986 did. We used propensity methods to match patient groups and parametric multiphase hazard methods to assess long-term survival. Our main outcome measures were postoperative morbidity complications, in-hospital mortality, and long-term survival.
- **Results** Witnesses had fewer acute complications and shorter length of stay than matched patients who received transfusions: myocardial infarction, 0.31% vs 2.8% ($P = .01$); additional operation for bleeding, 3.7% vs 7.1% ($P = .03$); prolonged ventilation, 6% vs 16% ($P < .001$); intensive care unit length of stay (15th, 50th, and 85th percentiles), 24, 25, and 72 vs 24, 48, and 162 hours ($P < .001$); and hospital length of stay (15th, 50th, and 85th percentiles), 5, 7, and 11 vs 6, 8, and 16 days ($P < .001$). Witnesses had better 1-year survival (95%; 95% CI, 93%-96%; vs 89%; 95% CI, 87%-90%; $P = .007$) but similar 20-year survival (34%; 95% CI, 31%-38%; vs 32% 95% CI, 28%-35%; $P = .90$).
- **Conclusions** Witnesses do not appear to be at increased risk for surgical complications or long-term mortality when comparisons are properly made by transfusion status. Thus, current extreme blood management strategies do not appear to place patients at heightened risk for reduced long-term survival.

Blood transfusion rates are declining in the United Sates as clinicians are adopting more restrictive transfusion strategies.

Blood Product Conservation is Associated with Improved Outcomes and Reduced costs after Cardiac Surgery

Damien J. LaPar, MD, MSc, Ivan K. Crosby, MD, Gorav Ailawadi, MD,a Niv Ad, MD,b Elmer Choi, MD, Bruce D. Spiess, MD, Jeffery B. Rich, MD,d Vigneshwar Kasirajan, MD, Edwin Fonner, Jr, DrPH, Irving L. Kron, MD, and Alan M. Speir, MD,b Investigators for the Virginia Cardiac Surgery Quality Initiative

Background: Efforts to reduce blood product use have the potential to avoid transfusion-related complications and reduce health care costs. The purpose of this investigation was to determine whether a multi-institutional effort to reduce blood product use affects postoperative events after cardiac surgical operations and to determine the influence of perioperative transfusion on risk-adjusted outcomes.

Methods: A total of 14,259 patients (2006-2010) undergoing nonemergency, primary, isolated coronary artery bypass grafting operations at 17 different statewide cardiac centers were stratified according to transfusion guide- line era: pre-guideline (n 1⁄4 7059, age 1⁄4 63.7 ` 10.6 years) versus post-guideline (n 1⁄4 7200, age 1⁄4 63.7 ` 10.5 years). Primary outcomes of interest were observed differences in postoperative events and mortality risk- adjusted associations as estimated by multiple regression analysis.

Results: Overall intraoperative (24% vs 18%, P<.001) and postoperative (39% vs 33%, P<.001) blood product transfusion were significantly reduced in the post-guideline era. Patients in the post-guideline era demonstrated reduced morbidity with decreased pneumonia (P 1⁄4 .01), prolonged ventilation (P 1⁄4 .05), renal failure (P 1⁄4 .03), new-onset hemodialysis (P 1⁄4 .004), and composite incidence of major complications (P 1⁄4 .001). Operative mortality (1.0% vs 1.8%, P<.001) and postoperative ventilation time (22 vs 26 hours, P<.001) were similarly reduced in the post-guideline era. Of note, after mortality risk adjustment, operations performed in the post-guideline era were associated with a 47% reduction in the odds of death (adjusted odds ratio, 0.57; P<.001), whereas the risk of major complications and mortality were significantly increased after intraoperative (adjusted odds ratio, 1.86 and 1.25; both P<.001) and postoperative (adjusted odds ratio, 4.61 and 4.50, both P<.001) transfusion. Intraoperative and postoperative transfusions were associated with increased adjusted incremental total hospitalization costs ($4408 and $10,479, respectively).

Conclusions: Implementation of a blood use initiative significantly improves postoperative morbidity, mortality, and resource utilization. Limiting intraoperative and postoperative blood product transfusion decreases adverse postoperative events and reduces health care costs. Blood conservation efforts are bolstered by collaboration and guideline development. (J Thorac Cardiovasc Surg 2013;145:796-804)

Summary

- Blood transfusions are associated with adverse outcomes.
- Current guidelines favor a restrictive transfusion strategy.
- Stored, allogeneic red blood cells may not improve oxygen transport to tissues.
- Blood conservation strategies may be the most beneficial intervention

Questions and Answers

The Transfusion Requirements in Critical Care Investigators (Hebert et al) performed a randomized, multicenter trial. Liberal and restrictive transfusion strategies utilized hemoglobin triggers of

A. < 12, < 8

B. < 10, < 7

C. <12, < 6

D. <10, < 8

E. < 12, < 7

The Transfusion Requirements in Critical Care Investigators (Hebert et al) performed a randomized, multicenter trial. Liberal and restrictive transfusion strategies utilized hemoglobin triggers of

A. < 12, < 8

B. < 10, < 7

C. <12, < 6

D. <10, < 8

E. < 12, < 7

The Transfusion Requirements in Critical Care Investigators (Hebert et al) found that patients randomized to a restrictive strategy:

A. experienced improved survival.

B. experienced more ischemic complications.

C. experienced improved survival if more critically ill.

D. experienced improved survival if younger.

E. experienced improved survival if older.

The Transfusion Requirements in Critical Care Investigators (Hebert et al) found that patients randomized to a restrictive strategy:

A. experienced improved survival.

B. experienced more ischemic complications.

C. experienced improved survival if more critically ill.

D. experienced improved survival if younger.

E. experienced improved survival if older.

Blood transfusion is associated with:

A. increased risk of infection.

B. decreased survival.

C. increased risk of myocardial infarction.

D. increased risk of lung injury.

E. all of the above.

Blood transfusion is associated with:

A. increased risk of infection.

B. decreased survival.

C. increased risk of myocardial infarction.

D. increased risk of lung injury.

E. all of the above.

No conflicts to report

Supplemental References

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Coagulopathy

in

Critical Care Settings

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Reports no commercial interest

Agenda

- Brief review of hemostasis
- Review of laboratory testing
- General review of management and available hemostatic products
  - DIC
  - Anticoagulant reversal

Treat the bleeding patient not numbers. An elevated PT or PTT does not mandate treatment if there is no bleeding.

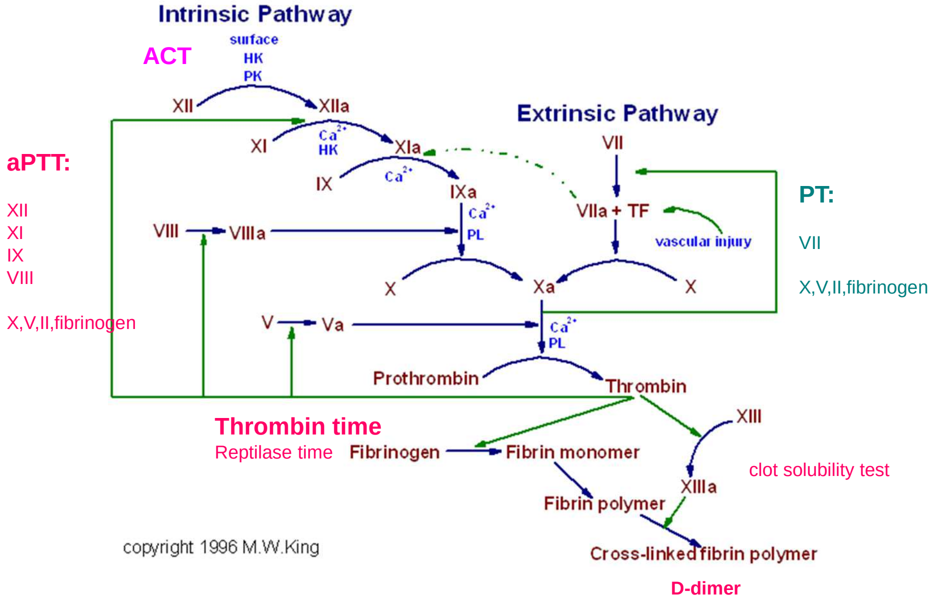
Requirements for Hemostasis

- **Primary hemostasis= Platelets and vWF**
  - Vessel wall
  - Platelets
  - vWF
- **Secondary hemostasis= Coagulation Factors**
  - Activation of coagulation factors: intrinsic/extrinsic paths
    - “coagulation cascade”
    - Activated platelets supply calcium and phospholipid surface to anchor and orient factors
  - Thrombin generation
  - Formation of cross-linked fibrin monomers to anchor thrombus and close large holes in vessel wall
- **Tertiary hemostasis**
  - Clot retraction
  - Cross linking of fibrin monomers by FXIII
- **Ideally: normal body temperature, normal pH, normal Ca++**

Approach to Evaluation

- **History**
  - Acquired versus inherited
- **Physical**
  - Type and location of bleeding
    - Diffuse oozing
    - Ecchymosis, petechiae
    - Surgical site
- **Laboratory tests**
  - CBC and review of peripheral smear
  - PT
  - PTT
  - Fibrinogen, D-dimer

Coagulation Tests and Coagulation Cascade



Intrinsic Pathway

ACT

surface
HK
PK

XII
XIIa
XI
Ca2+
HK
XIa
IX
Ca2+
IXa
Ca2+
PL

Extrinsic Pathway

VII
VIIa + TF
vascular injury

aPTT:

XII
XI
IX
VIII

X,V,II,fibrinogen

VIII
VIIIa
X
Xa
X
V
Va
Ca2+
PL

PT:

VII

X,V,II,fibrinogen

Prothrombin
Thrombin
XIII

Thrombin time

Reptilase time

Fibrinogen
Fibrin monomer
Fibrin polymer
XIIIa

clot solubility test

Cross-linked fibrin polymer

D-dimer

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High PT Normal aPTT

- **Inherited**
  - Factor VII deficiency
- **Acquired**
  - Vitamin K deficiency
  - Warfarin use
  - FVII inhibitor
  - Liver disease (early)

Normal PT High aPTT

- **Inherited**
  - FVIII, FIX, FXI, FXII deficiency
  - vWD

- **Acquired**
  - Specific factor inhibitor
  - Antiphospholipid antibody
  - heparins

High PT High aPTT

- **Inherited: rare**
  - Dysfibrinogenemia
  - Hypofibrinogenemia
  - Even more rare
    - Thrombin, V, X deficiency
- **Acquired**
  - Significant hemodilution
  - Inhibitor of thrombin, V, X
    - Tumor, amyloid, paraproteins
  - Supratherapeutic heparin, warfarin, DTIs
  - Antiphospholipid antibody
  - **Liver disease**
  - Consumptive coagulopathies
    - **DIC**
    - Cavernous hemangiomas

Evaluation

- **Elevated PT only**
  - Factor VII level
  - Mixing study on PT
- **Elevated aPTT only**
  - Mixing study
    - Corrects: Factor deficiency: specific factor levels
    - No correction: Inhibitor: lupus anticoagulant, specific factor inhibitor
- **Both PT and aPTT elevated**
  - Fibrinogen
  - D-dimer
  - Drug effect

Management of Coagulopathy

- **Establish diagnosis**
- Supportive care
- Severity of bleeding, need for procedures affects treatment decisions
- In general
  - Fibrinogen > 100-200 mg/dL
  - Platelets >20-30 x 10^9/L
  - Need for "normal" aPTT or PT?

Plasma

- FFP or TP
  - Contains all clotting and anti-clotting factors at normal plasma concentration
  - 70 kg person has 2.8 liters plasma
  - "Normal" PT and aPTT require factor levels >30%
  - Each bag of plasma approx 250 ml (180-300)
  - To obtain a 30% level when starting at <1% will require 4 to 6 bags of FFP or approximately 20 ml/kg or 1000-1500 ml of plasma

Cryoprecipitate

- Contains:
  - **Fibrinogen**
  - **vWF and FVIII**
  - **FXIII**

  - Obtained from 1 unit whole blood
    - Cold insoluble fraction of high mw proteins as thawing FFP
    - resuspended in 15 ml plasma = 1 unit cryo
    - Minimum **80** IU FVIII and **150** mg fibrinogen

  - BWH: One order of cryo = 2 bags* =10 units of cryo
    - Each bag is pool of 5 donors

Adverse effects of FFP and cryo

- FFP: volume and infusion time
- Allergic
- TRALI—USA now uses only male donors for plasma
- TACO—Transfusion associated circulatory overload
- ABO type specific
- Pathogens--processed, pasteurized, solvent-detergent treated products

Fibrinogen Concentrate

- " RiaSTAP" FDA approved for use in 2009
- Fibrinogen concentrate made from pooled plasma
  - Heat treated, lyophylized
- Labeled indication for hypo- or afibrinogenemia, not dysfibrinogenemia
- Other off label use:
  - Acquired hypofibrinogenemia
  - Obstetric hemorrhage including post-partum hemorrhage
  - Post-operative hemorrhage
  - Trauma-associated hemorrhage

  - Increasingly used in Europe due to concerns for CJD from plasma

PCC

- Prothrombin Complex Concentrates
  - II, VII, IX, X
  - Much smaller volume than FFP or cryo
  - Data for warfarin reversal
  - Data for efficacy with rivaroxaban
  - No response with dabigatran

- **4 factor**: Contains adequate/equal amounts of all
  - Dosed on FIX activity
  - Standard 20-50 IU/kg depending on factor levels, INR
  - **Kcentra**: FDA approved April 2013
    - Contains small amount of heparin. Do not use in patients with HIT
- **3 factor**: Contains lower level of F VII
    - Requires some FFP

FEIBA

- Factor Eight Inhibitor Bypassing Activity
  - – Developed for hemophilia A patients with inhibitors to factor VIII
    - Contains factors II, IX, and X and activated VII
  - – "activated" prothrombin complex concentrate
  - – Potentially less thrombotic risk than rVIIa

rVIIa

- Recombinant activated VII product
  - – Novoseven
- Favored antidote for all bleeding despite lack of data
- Cost has caused many institutions to limit use
- Some risk of thrombosis, as with FEIBA
  - – Older patients most at risk OR 2.4-3

Levi *NEJM* 2010

DIC--Etiology

- **Increased Tissue Factor**
  - Injured tissue
    - trauma
    - tissue necrosis
    - burns
  - Stimulated monocytes or endothelial cells
    - endotoxin
    - cell wall polysaccharides
    - immune complexes
  - Endothelial sloughing from acidosis
- **Thrombogenic Phospholipids**
  - Obstetric disorders
    - abruptio placentae
    - eclampsia
    - amniotic fluid embolism
  - Intravascular hemolysis
    - transfusion reactions
    - infections
  - Ascitic fluid
    - Leveen or Denver shunts

DIC—Clinical Presentation

- **Bleeding**
  - More pronounced in liver disease
  - Wound bleeding
  - Waterhouse-Friderichsen Syndrome
- **Thrombosis (microvascular)**
  - Organs at risk
    - Lungs (ARDS)
    - Kidneys (ARF)
    - Liver
    - Cardiac (MI)
    - Brain (stroke)
  - Purpura fulminans
    - gangrene of digits or skin necrosis

DIC--Management

- **Management**
  - **Identify and treat underlying condition**
  - **Supportive care**
    - If underlying condition rapidly reversible, watch and wait if patient not bleeding
    - use FFP, cryo, and platelets as needed
    - **Treat bleeding not numbers**
      - Fibrinogen >100-200, plts >20-30k, higher if bleeding
  - **Stop microvascular thrombosis?**
    - **consider** heparin, tPA, or urokinase
      - Role more established in chronic DIC
      - Low dose 4-5 U/kg IV UFH
      - **No mortality benefit**

DIC--Management

- Control bleeding, use FFP, cryo, platelets as needed
  - RiaStap: fibrinogen concentrate
  - Kcentra: II, VII, IX, X, proteins S and C (4-PCC)

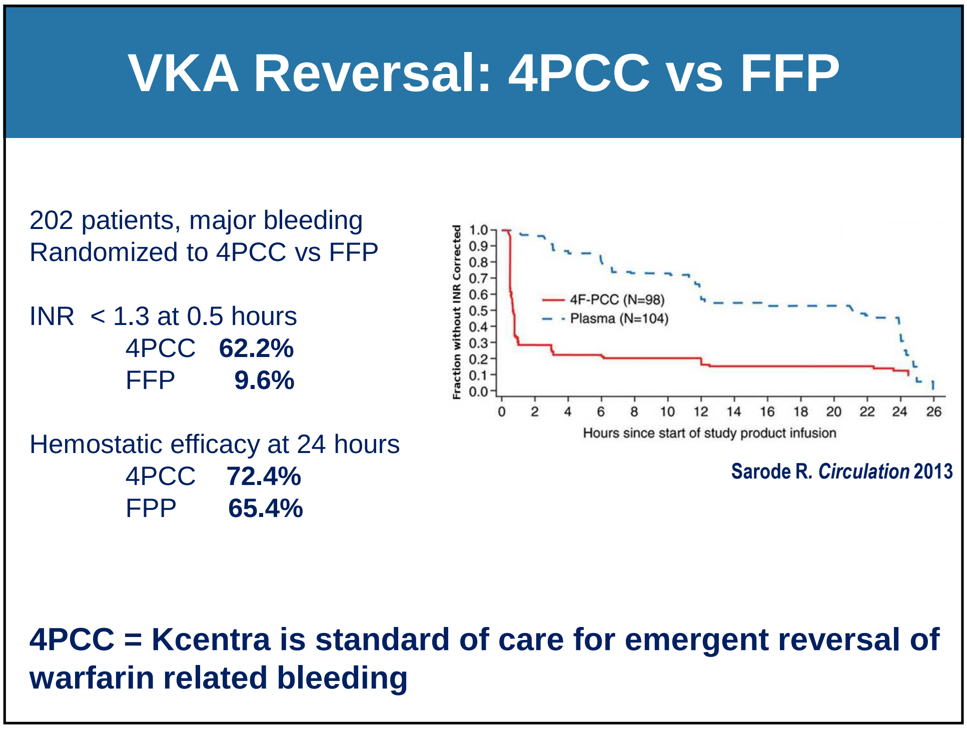
- Role for natural anticoagulant products?
  - **No mortality benefits have been shown for any**
    - Antithrombin
    - Activated protein C (drotrecogin/Xigris)
    - Recombinant thrombomodulin
    - TFPI
    - Other investigational agents: MAPK,IL-10,NAPc2

Anticoagulant Related Bleeding

- **Heparins**
  - UFH: protamine
  - LMWH: protamine
  - Fondaparinux: extremely limited data for rVIIa
- **Warfarin**
  - Vitamin K, FFP, PCC
- **Parenteral DTIs** (bivalirudin, argatroban)
  - Time
- **New oral anticoagulants**
  - idarucizumab for life threatening dabigatran related bleeding or urgent surgery
  - 4 PCC
  - Other antidotes in development

VKA Reversal

- **Options for VKA reversal:**
  - **Replace missing factors**
  - Vitamin K
  - FFP
  - Prothrombin complex concentrates (PCC)
    - Non-activated vs activated
- **Need for reversal? Is patient bleeding?**
- **No:**
  - INR 4-10: hold warfarin
  - INR greater than 10: hold warfarin and judicious use of vitamin K



VKA Reversal: 4PCC vs FFP

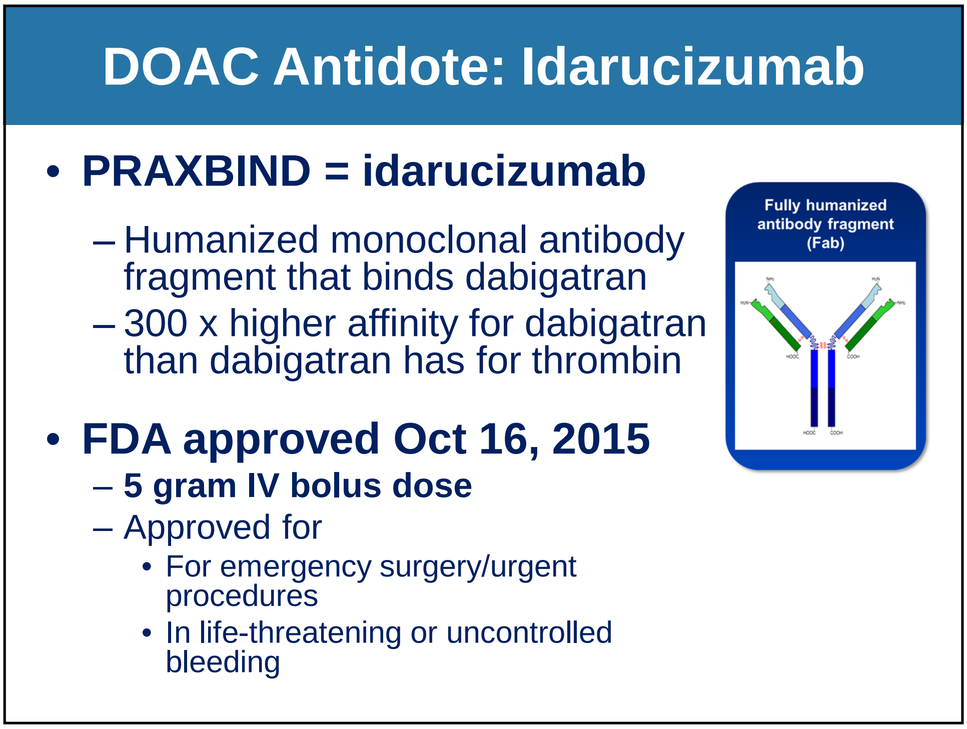
202 patients, major bleeding
Randomized to 4PCC vs FFP

INR < 1.3 at 0.5 hours
4PCC **62.2%**
FFP **9.6%**

Hemostatic efficacy at 24 hours
4PCC **72.4%**
FPP **65.4%**

Sarode R. *Circulation* 2013

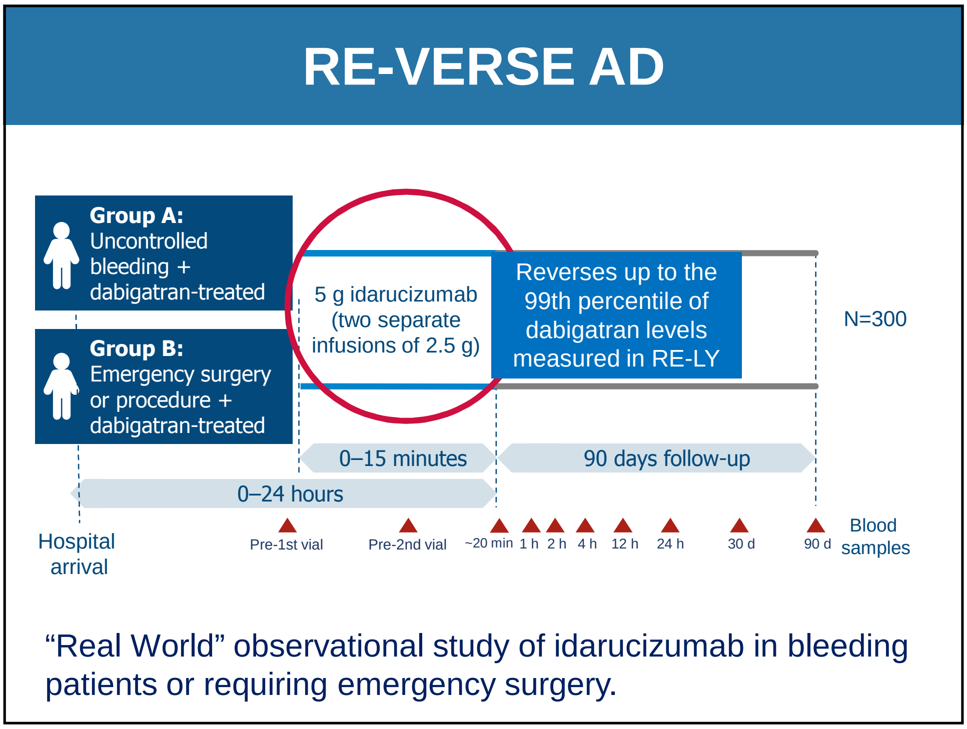
4PCC = Kcentra is standard of care for emergent reversal of warfarin related bleeding



DOAC Antidote: Idarucizumab

- **PRAXBIND = idarucizumab**
  - Humanized monoclonal antibody fragment that binds dabigatran
  - 300 x higher affinity for dabigatran than dabigatran has for thrombin
- **FDA approved Oct 16, 2015**
  - **5 gram IV bolus dose**
  - Approved for
    - For emergency surgery/urgent procedures
    - In life-threatening or uncontrolled bleeding

Fully humanized antibody fragment (Fab)



RE-VERSE AD

Group A: Uncontrolled bleeding + dabigatran-treated

Group B: Emergency surgery or procedure + dabigatran-treated

5 g idarucizumab (two separate infusions of 2.5 g)

Reverses up to the 99th percentile of dabigatran levels measured in RE-LY

N=300

0–15 minutes

90 days follow-up

0–24 hours

Hospital arrival

Pre-1st vial

Pre-2nd vial

~20 min

1 h

2 h

4 h

12 h

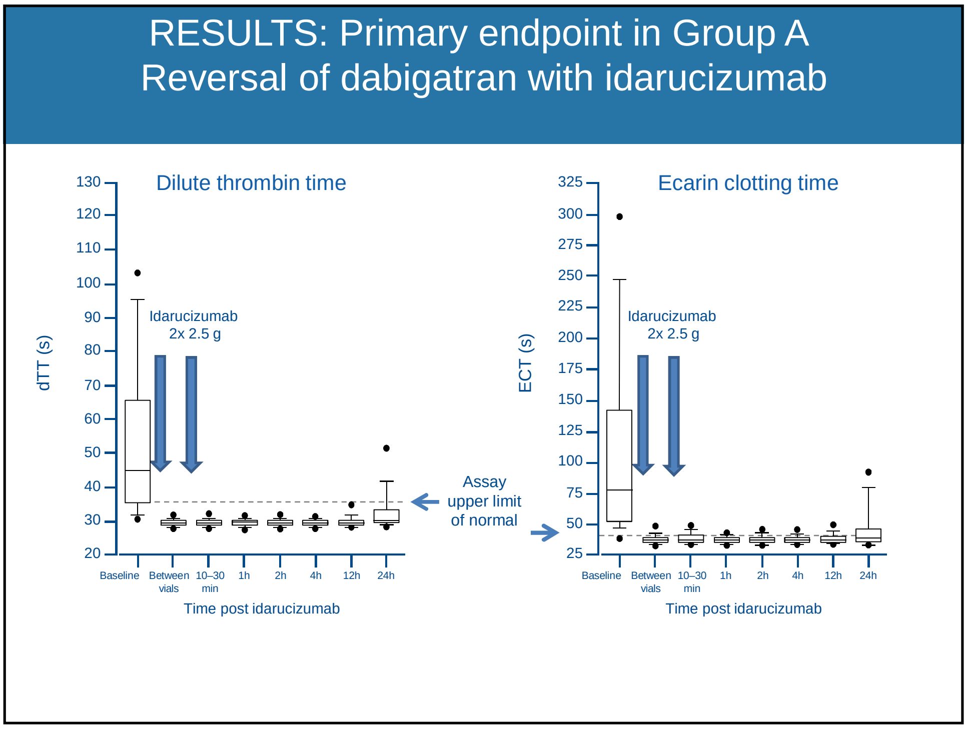
24 h

30 d

90 d

Blood samples

“Real World” observational study of idarucizumab in bleeding patients or requiring emergency surgery.



RESULTS: Primary endpoint in Group A Reversal of dabigatran with idarucizumab

RE-VERSE AD

Primary endpoint: maximal reversal of dabigatran based on lab tests within 4 hours: achieved in 100%

- “Normal” hemostasis in >90% undergoing surgery
- Hemostasis achieved by 11 hours in bleeding patients

- 18 deaths, half > 96 hours after idarucizumab, due to underlying conditions
- 5 thrombotic events, 1 within 72 hrs

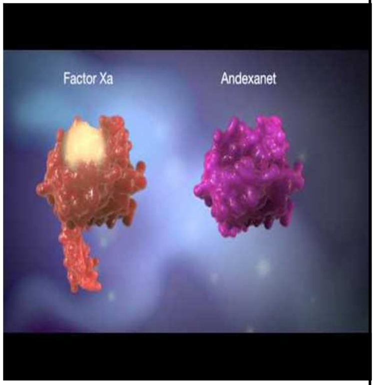
- **Continued support of study, goal 300 patients**

DOAC Antidote: andexanet alfa

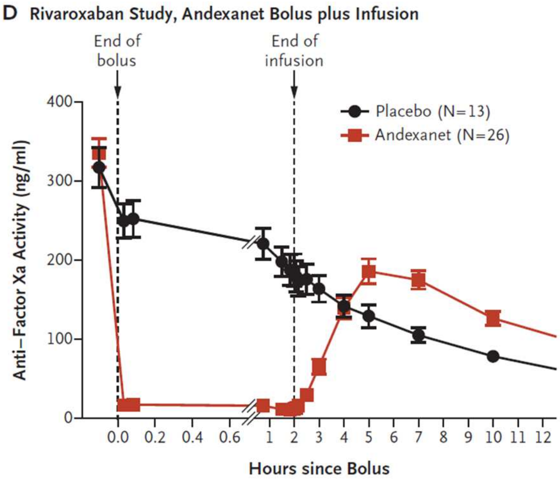
AndexXa = andexanet alfa

- “decoy” recombinant **FXa** molecule with mutation in catalytic site, lacks Gla domain
- “universal” Fxai antidote
- Recent release of interim analysis of real world study

  --NEJM Aug 2016
- Not yet FDA approved for use



ANNEXA-R



ANNEXA-4

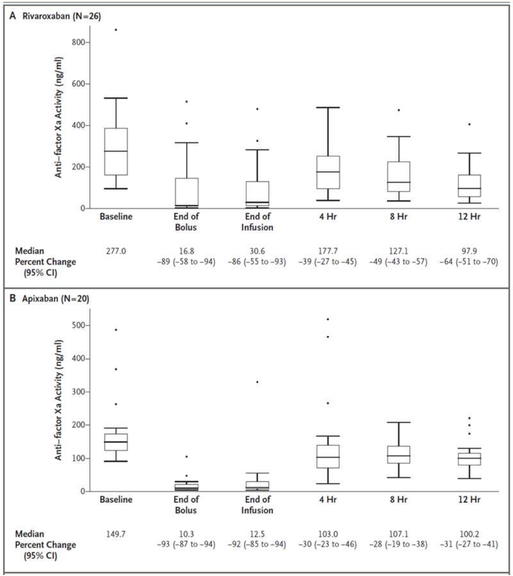
Annexa-4: phase 3b/4 "real world study"

- active major bleeding in patients taking apixaban, rivaroxaban, edoxaban, or enoxaparin
- 2 hour continuous infusion after bolus
- Patients requiring surgery within 12 hours excluded

fXa Inhibitor	IV Bolus	IV Infusion
All patients receiving apixaban and those patients who received rivaroxaban >7 hours ago	400 mg at a target rate of 30 mg/min	480 mg @ 4 mg/min for 120 minutes
Patients who received enoxaparin or a dose of rivaroxaban within ≤ 7 hours or at an unknown time* *if there is a delay between medical presentation and start of andexanet of more than 7 hours, the patient should receive the dose for rivaroxaban >7 hours ago	800 mg at a target rate of 30 mg/min	960 mg @ 8 mg/min for 120 minutes

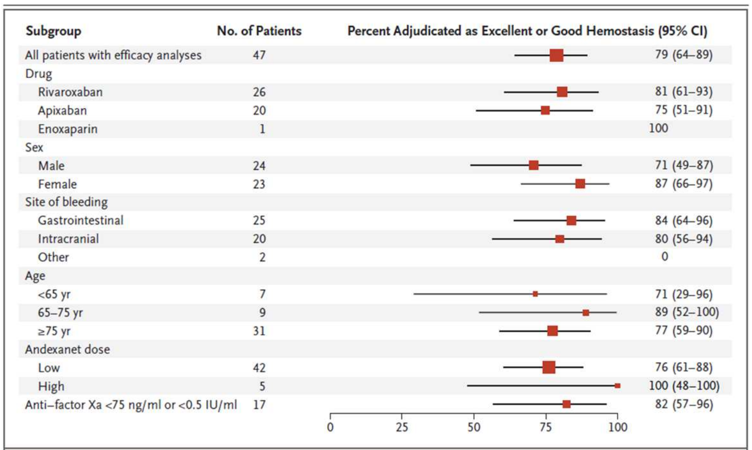
ANNEXA-4

Interim analysis of “real world” study released Aug 2016



Connolly NEJM Aug 30 2016

ANNEXA-4



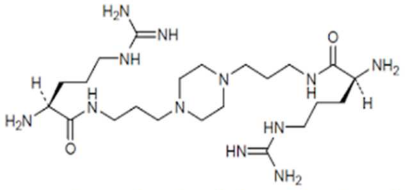
Subgroup	No. of Patients	Percent Adjudicated as Excellent or Good Hemostasis (95% CI)
All patients with efficacy analyses	47	79 (64–89)
Drug		
Rivaroxaban	26	81 (61–93)
Apixaban	20	75 (51–91)
Enoxaparin	1	100
Sex		
Male	24	71 (49–87)
Female	23	87 (66–97)
Site of bleeding		
Gastrointestinal	25	84 (64–96)
Intracranial	20	80 (56–94)
Other	2	0
Age		
<65 yr	7	71 (29–96)
65–75 yr	9	89 (52–100)
≥75 yr	31	77 (59–90)
Andexanet dose		
Low	42	76 (61–88)
High	5	100 (48–100)
Anti–factor Xa <75 ng/ml or <0.5 IU/ml	17	82 (57–96)

Figure 2. Subgroup Analysis of Hemostatic Efficacy.

Connolly NEJM Aug 30 2016

Antidote: ciraparantag

- **Reversal agent for ALL anticoagulants:**
  - DTI, Xai, LMWH, fondaparinux.
  - Not warfarin or argatroban
- PER977: **aripazine** 500 Da cationic molecule binds through non-covalent bonds to anticoagulants
- Ciraparantag



- Dose dependent decrease in whole blood clotting time following edoxaban in healthy volunteers

NEJM Nov 2014

Use of Antidotes

How should targeted reversal agents be used?

Life-threatening bleed

- intracranial hemorrhage, critical organ, massive hemorrhage
- Bleeding in the setting of delayed renal clearance or overdose

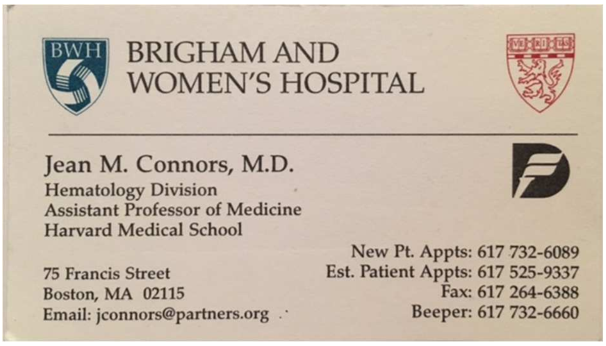
Emergency Surgery

Not for use in

- Elective surgery or surgery that can delayed
- elevated coag tests but no bleeding
- bleeding managed with routine supportive measures

Summary

- Coagulation abnormalities are frequently seen in the ICU and are usually acquired as a result of underlying disease process.
- Treatment of primary disorder is often sufficient to restore normal levels, although transfusion support with appropriate blood products and factor concentrates may be required.
- Specific reversal agents for anticoagulants are available, but improvement in outcomes not yet demonstrated.



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Question 1

72 yo man with past medical history of hypertension, coronary artery disease, and congestive heart failure, is admitted to ICU with hematemesis. Hematocrit is 25%, previously 39% 4 months ago. Systolic pressure is 90, heart rate 120. INR 9.2.

He is on warfarin for atrial fibrillation without history of prior thromboembolic events. He just finished a course of trimethoprim/sulfamethoxazole for a urinary tract infection. He took warfarin last night.

Question 1

In addition to red cell support and EGD, you plan to manage elevated INR with the following plan:

a. Hold warfarin and observe. He has finished TMP/SMZ and INR will drift down
b. Give vitamin K 1 mg oral dose.
c. Give FFP at 20 ml/kg, or 6 bags.
d. Give 4 factor prothrombin complex concentrate at 50 U/kg FIX activity and 10 mg vitamin K IV.
e. Give recombinant activated factor VII.

Question 1

Correct answer: d

This patient has significant hematocrit drop and is hemodynamically unstable. He requires rapid reversal of warfarin to decrease further bleeding. Holding warfarin or giving low dose of oral vitamin K are insufficient. In addition to lengthy administration time, the volume load of approximately 1500 ml of plasma may be difficult to tolerate in this patient with a history of CHF. Limited data support the use of rVIIa and given age and history of CAD there is concern for prothrombotic effects. Four factor PCC is the most appropriate treatment.

Question 2

An 85 year old woman is admitted at 11 am with severe abdominal pain. Evaluation and imaging are concerning for ischemic bowel. She has atrial fibrillation and is taking dabigatran 75 mg twice daily as her creatinine clearance is 28 mL/min. She took dabigatran at 7 am.

The consulting surgeon determines that surgery is needed in the next 2 hours, and asks what to do about dabiagtran. You suggest:

A. There is no need to reverse anticoagulation as she is on a reduced dose of dabiagtran
B. Give FFP as the INR is elevated
C. Give idarucizumab 5 grams IV bolus
D. Insist that surgery be delayed for 24 hours
E. Give FEIBA according to package insert

Question 2

Answer C

This elderly woman has ischemic bowl and renal insufficiency. Plasma dabigatran concentration is likely still at its peak as it has been only 4 hours since the last dose. Delaying surgery for another 24-48 hours is not an option.

Idarucizumab is FDA approved for this indication and should be used. Other options such as FFP or FEIBA are not acceptable or not adequate to reverse the anticoagulant effects of dabigatran.

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Acute Kidney Injury and Renal Replacement Therapy

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Conflict of Interest Disclosure Slide

- I have no financial relationships with commercial entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients relevant to the content I am presenting.

- **ARF/AKI in the ICU**
- When to initiate RRT in ARF/AKI
- Does dose matter?
- Does Modality matter?

Background

- Incidence of Acute Kidney Injury in ICU = 6%
- 73% of these patients with Acute Kidney Injury require Renal Replacement
- In-hospital mortality still remains ~50%

Acute Kidney Injury in the ICU

- Large worldwide prospective observational study of 54 ICUs
- The most common contributing factor to Acute Kidney Injury was septic shock (47.5%).
- 30% of patients had preadmission renal dysfunction.
- Overall hospital mortality was 60.3%
- Independent risk factors for hospital mortality included
  - vasopressors
  - mechanical ventilation
  - septic shock
  - cardiogenic shock
  - hepatorenal syndrome

Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T.) Uchino S. JAMA. 2005;294(7):813-8

RIFLE Criteria

Acute Dialysis Quality Initiative workgroup 2004

- 3 levels of renal dysfunction
  - Risk of renal dysfunction
  - Injury to the kidney
  - Failure of kidney function
- 2 levels of outcome
  - Loss of kidney function
  - End-stage kidney disease

Predictive value of RIFLE

- An almost linear relationship between RIFLE severity and mortality.
- Retrospective single-center trial 20,126 patients
- Hospital mortality for the groups was
  - 4.4% for Normal patients
  - 15.1% for Risk patients
  - 29.2% for Injury patients
  - 41.1% for Failure patients.
- All RIFLE criteria were significant predictive factors for hospital mortality, with an increase in odds ratios with severity.

Uchino S. Crit Care Med 2006;34(7):1913-7.

Biomarkers

- A reliable marker of early kidney injury in serum or urine has yet to be clinically validated and widely used.
- Candidates under investigation
  - NGAL
  - NAG
  - cystatin C
  - IL-18
  - kidney injury molecule 1

Sepsis Acute Kidney Injury

- Dynamic changes of serum creatinine in the first 24 h of ICU admission has major prognostic significance
- AKI in patients with SIRS can be predicted at the onset of sepsis on the basis of older age, elevated serum creatinine, elevated central venous pressure, and liver failure
- Emerging data supports a more “nephrotoxic” (cytokine-mediated) mechanism of injury rather than “ischemic”
- Optimization of renal perfusion may be a factor for prevention and treat AKI in sepsis
- No accepted pharmacologic or extracorporeal treatment is in use
- Mortality of septic AKI (73%) far higher than nonseptic AKI (45%)

Contrast-Induced Acute Kidney Injury

- Contrast-induced AKI is associated with increased 30-day and overall mortality
- Higher mortality risk in patients who developed contrast-induced AKI after intravenous contrast administration as compared with intra-arterial
- **Prevention**
- low-osmolar contrast media better than high-osmolar
- IV fluids better than oral hydration prior to procedure
- N-acetylcysteine Unclear benefit but low-risk profile and low cost
- NaHCO3 Unclear benefit over saline
- Hemodialysis insufficient evidence

Acute Decompensated Heart Failure (ADHF)

- Chronic Kidney Disease or Acute Kidney Injury are shown to be associated with adverse outcomes during treatment of ADHF
- Mixed results of trails comparing ultrafiltration with diuretics in ADHF
- **Volume overload Treatment**
- No apparent advantage of ultrafiltration over diuretic therapy.
- Negative Large RCT on Nesiritide in Decompensated Heart Failure
  - N Engl J Med 2011; 365:32-43

Acute Kidney Injury following Cardiac Surgery

- Perioperative use of aprotinin (serine protease inhibitor with antifibrinolytic properties) increases the risk for AKI and adverse outcomes after cardiac surgery
- **Prophylaxis in Cardiac Surgery**
- Fenoldopam mesylate (dopamine type 1 receptor agonist) negative trial
  - JAMA. 2014;312(21):2244-2253
- N-acetyl-cysteine prophylaxis trials have not shown benefit
- Mannitol – small studies suggest no utility

Hepatorenal Syndrome

- Volume unresponsive, refractory prerenal azotemia in patients with chronic liver disease, characterized by systemic and splanchnic vasodilation but profound renal vasoconstriction without parenchymal kidney injury.
- Prognosis of HRS type 1 without liver transplantation is so poor that therapy is futile
- **Prevention/ Treatment**
- Small studies suggest efficacy of a combination of albumin and terlipressin therapy in improving renal function in HRS but did not address clinical outcomes
- Small studies suggest that norepinephrine may offer similar potential benefit to terlipressin

Rhabdomyolysis

- Blood (myoglobin) by dipstick, no RBCs on microscopic examination, presence of pigmented casts
- Aggressive volume replacement.
- Traumatic rhabdomyolysis, fluid resuscitation before the crushed extremity is released.
- Urinary alkalinization may increase the solubility of heme proteins within the tubule.
- Alkalinization may decrease the redox cycling of myoglobin, thereby reducing the generation of reactive oxygen species.
- The use of mannitol is no better than expansion with saline.
- No benefit for dopamine, furosemide, or N-acetylcysteine in this setting.

Atheroembolic disease

- Delayed development of AKI after an angiographic procedure, or AAA repair accompanied by symptoms of systemic atheroembolization.
- Muscle, GI, CNS involvement
- White blood cells in urine, white blood cell casts.
- High likelihood of dialysis requirement (35%)
- High likelihood of dialysis dependence (25%)

Abdominal Compartment Syndrome

- Oliguric acute renal failure after abdominal trauma in a patient who has required aggressive volume resuscitation.

- Intra-abdominal hypertension: intra-abdominal pressure of >12 mmHg on three measurements obtained 4 to 6 h apart
- Abdominal Compartment Syndrome is defined as the presence of an intra-abdominal pressure of >20mmHg that is associated with a single or multiple organ system failure that was not previously present

- The treatment of abdominal compartment syndrome is abdominal decompression.

Acute Interstitial Nephritis

- Hypersensitivity reaction (PCN, sulfa, NSAIDs most common)
- Inflammatory cells in renal interstitium leading to tubular damage
- Retrospective study 2600 patients do not support the routine administration of corticosteroid therapy in the management of Acute Interstitial Nephritis
- Mycophenolate mofetil may be a useful therapeutic option for steroid-resistant or -intolerant Acute Interstitial Nephritis

Renal Recovery

- No way to predict when/if patient will recover
- Longer period of renal replacement (>3 weeks) the less likely recovery occurs
- Long term recovery > 6 weeks is possible
- Repopulation of damaged renal tubules:
  - Proliferation of tubular epithelial cells and resident renal-specific stem cells
  - Role for paracrine factors from bone marrow– derived mesenchymal stem cells

- Growth factors have important role in the repair process in animal models of renal injury
  - IGF, hepatocyte growth factor, and erythropoietin

- ARF/AKI in the ICU
- **When to initiate RRT in ARF/AKI**
- Does Modality matter?
- Does dose matter?

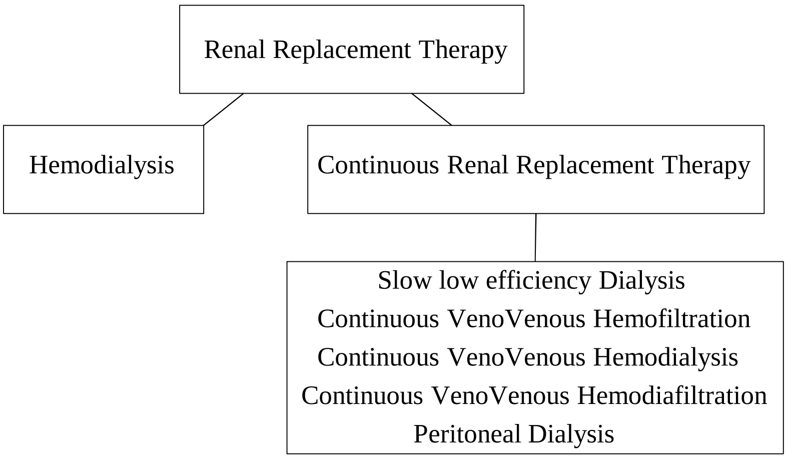
Primary Therapeutic Goals in Acute Kidney Injury

- Optimize hemodynamic and volume status
- Minimize further renal injury
- Correct metabolic abnormalities
- Removal of Uremic toxins
- Permit adequate nutrition

Luyckx VA Semin Dial. 2004;17(1):30-6.

Absolute Indications for Renal Replacement

- Volume overload unresponsive to diuretic therapy,
- Severe hyperkalemia or unresponsive to medical intervention
- Metabolic acidosis unresponsive to medical intervention
- Overt uremic manifestations



Renal Replacement Therapy

Hemodialysis

Continuous Renal Replacement Therapy

Slow low efficiency Dialysis
Continuous VenoVenous Hemofiltration
Continuous VenoVenous Hemodialysis
Continuous VenoVenous Hemodiafiltration
Peritoneal Dialysis

Hemodialysis

- Blood pumped from patient to Filter with large surface area 4 hrs / 48h
- Purpose
  - Fast Solute removal (Cr, BUN, K, toxins) or solute addition (HCO_3)
  - Water removal (125-1000 ml/hr)
- Diffusion
  - Solutes removed or added with diffusion down concentration gradient of dialysate.
  - Patient K 6, dialysate K set at 2, favors K removal
  - Patient HCO_3 15, dialysate HCO_3 35, favors HCO_3 addition
- Ultrafiltration
  - Water removal via negative pressure
- Toxins/drugs removed if in circulation, small, not protein bound

Continuous Renal Replacement

- Blood pumped from patient to Filter with large surface area 24 hours/d
- Purpose
  - Slow solute removal (Cr, BUN, K, toxins) or solute addition (HCO_3)
  - Slow Water removal (25-150 ml/ hr)
- Convection
  - Solutes continuously removed via negative pressure
  - Water continuously removed via negative pressure
  - Replacement solution given with Na, Cl, HCO_3, K, Mg, dextrose
  - PO_4, Ca supplementation
- Toxins/drugs removed if in circulation, small, not protein bound

Primary Therapeutic Goals in Continuous Renal Replacement Therapy

- Solute Removal
  - Diffusion and Convection
- Solute Addition
  - Replacement Fluid
- Fluid Removal
  - Convection
- Detoxification

Acute Dialysis Quality Initiative Workgroup

- The ADQI working group found variations of up to two-fold in the reported levels of urine output, blood urea nitrogen, and serum creatinine at the time of initiation of RRT
- Uncertainty exists as to when to begin renal replacement therapy
- Complications of chronic renal failure may have more severe consequences for critically ill patients with Acute Kidney Injury, RRT should start prior to these complications.

Kellum JA et al. Kidney Int 2002;62(5):1855-63.

Timing of Initiation of Dialysis in Critically Ill Patients with Acute Kidney Injury

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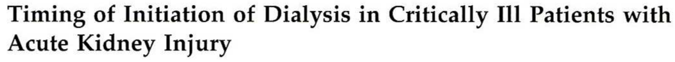
- Large multicenter observational study of Acute Kidney Injury in critically ill patients
- Analysis of dialysis initiation from PICARD
  - Observational cohort study of 618 patients with Acute Kidney Injury in intensive care units at five academic medical centers in the United States.
- 243 patients who had eGFR>30 on admission who required dialysis for AKI
- Examined risk for death within 60 days from the diagnosis of AKI by the BUN at the start of dialysis in a low azotemia group BUN<=76mg/dl and a high azotemia group BUN>76mg/dl

Clin J Am Soc Nephrol. 2006;1(5):915-9.



Timing of Initiation of Dialysis in Critically Ill Patients with Acute Kidney Injury

Results
Timing of Dialysis Initiation and Mortality

- Adjusted for age, hepatic failure, sepsis, thrombocytopenia, and serum creatinine and stratified by site and initial dialysis modality, the relative risk for death associated with high BUN at IHD initiation
  - RR=1.85(95% CI 1.16 to 2.96)

Clin J Am Soc Nephrol. 2006;1(5):915-9.

Creatinine and Critical Illness

- Serum creatinine values (Cr) directly affect assessment and classification of patients with AKI, time of initiation of Continuous Renal Replacement Therapy (CRRT), and prognosis in the critically ill.
- Investigations have demonstrated that even small increases in serum creatinine are related to worse outcomes in heterogeneous hospitalized populations.

Creatinine and Critical Illness

- Serum Creatinine values depend on age, gender, race, volume status, protein intake and lean muscle mass.
- Serum creatinine values are proposed as a surrogate indicator of nutritional status.
- Thus, higher serum creatinine values or the capacity to generate creatinine may be related to better health status and survival in the critically ill.
- Conversely, Creatinine of ≤0.6 mg/dL increases in hospital mortality in critically ill patients.

In severe acute kidney injury, a higher serum creatinine is paradoxically associated with better patient survival

- 134 patients
- Medical 43%, Surgical 22%, Cardiac surgery 35%
- Survival to hospital discharge 29.5 %

- A higher SCr on initiation of CRRT was associated with better survival controlling for selected covariates (OR 1.438, 95% CI 1.034–1.999).
- Adjustment of the model by preadmission CKD and severity of disease, respectively decreased or annulled the significance of SCr levels.

- Higher creatinine is an indicator of better nutrition and muscle mass

Cerdá J, Cerdá M, Kilcullen P, Jayne Prendergast J. Nephrol Dial Transplant. 2007;22(10):2781-4.

- ARF/AKI in the ICU
- When to initiate RRT in ARF/AKI
- **Does Modality matter?**
- Does dose matter?

Does Modality matter?

- Intermittent Hemodialysis
- Sustained Low Efficiency Dialysis
- Sustained Low Efficiency Hemofiltration
- CVVH
- CVVHDF
- CVVHD
- HVHF
- PD
- Current data do not provide objective criteria for selection among these modalities in the majority of patients

CRRT Clinical Practice

- Large worldwide prospective observational study of 54 ICUs
- Of those requiring RRT for Acute Kidney Injury in ICU:
  - 80% placed on CRRT
  - 17% placed on IHD
  - 52.8% CVVH
  - 34.0% CVVHDF
  - 33.1% No anticoagualtion

Uchino et al. Int Care Med. 2007;33(9):1563-70

Comparison of continuous and intermittent renal replacement therapy for acute renal failure

Dominik E. Uehlinger[1], Stephan M. Jakob[2], Paolo Ferrari[1], Markus Eichelberger[1], Uyen Huynh-Do[1], Hans-Peter Marti[1], Markus G. Mohaupt[1], Bruno Vogt[1], Hans Ulrich Rothen[2], Bruno Regli[2], Jukka Takala[2] and Felix J. Frey[1]

191 ICU patients with Acute Kidney Injury requiring RRT

Single Swiss center

70 patients randomized to CVVHDF

55 Patients randomized to IHD

Well matched demographics, cause of AKI, severity of illness

	ICU Mortality	Hospital Mortality
CVVHDF	34%	47%
IHD	38%	51%

97% of all surviving patients recovered renal function

Uehlinger DE et al. Nephrol Dial Transplant. 2005;20(8):1630-7.

Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial

- Prospective Randomized Multicenter Study non-blinded
- 21 French ICUs
- 360 pts randomized hemodialysis vs continuous venovenous hemofiltration, 37 pts crossed over, intention to treat analysis

- **No** difference in hemodialysis vs continuous venovenous hemofiltration

- Over the length of the study there were significant increases in survival rates in the IHD arm while the survival rate was the same for the CRRT arm.

Vinsonneau et al. Lancet 2006; 368: 379-85

Intermittent versus continuous renal replacement therapy for acute renal failure in adults

- RCTs comparing CRRT with IRRT in adult patients with Acute Kidney Injury and reporting pre-specified outcomes of interest were included.

- 15 studies identified (1550 patients).
- CRRT did not differ from HD with respect to:
  - in-hospital mortality (RR 1.01, 95% CI 0.92 to 1.12),
  - ICU mortality (RR 1.06, CI 0.90 to 1.26),
  - hemodynamic instability (RR 0.48, CI 0.10 to 2.28)
- Patients on CRRT were likely to have:
  - significantly higher MAP
  - higher risk of clotting dialysis filters

Rabindranath K, Cochrane Database of Systematic Reviews 2008 Issue 1

- ARF/AKI in the ICU
- When to initiate RRT in ARF/AKI
- Does Modality matter?
- **Does dose matter?**

RRT Dose

- Prospective trial of 160 patients enrolled in an alternating fashion treated with daily Hemodialysis and alternative day Hemodialysis treatment.
- Better uremia control, fewer hypotensive episodes, faster resolution of Acute Renal Failure, and lower mortality among those with daily IHD treatments versus alternate-day treatment.

Schiffl et al N Engl J Med. 2002 31;346(5):305-10.

RRT Dose

- Ronco et al showed benefit with higher doses of Continuous Renal Replacement Therapy.
- Randomly assigned 425 patients with Acute Renal Failure to receive ultrafiltration at 20 mL/h/kg, 35 mL/h/kg, or 45 mL/h/kg.
- Survival was significantly higher in the 35 mL/h/kg group and the 45 mL/h/kg group in comparison to the 20 mL/h/kg group

Ronco Lancet 2000;356(9223):26-30

RRT Dose

VA/NIH ATN Study

- The VA/NIH Acute Renal Failure Trial Network (ATN) Study is designed to clarify the optimal dose of RRT in critically ill patients with Acute Renal Failure.
- Multicenter, prospective, randomized, parallel-group trial of high-intensity vs low-intensity RRT in critically ill patients.
- Its primary study endpoint was 60-day all-cause mortality.
- The trial is designed to allow for patients to receive both CRRT and or IHD depending on changes in hemodynamic stability over time.

- **No** difference in mortality high vs low intensity RRT

Standard *versus* High-Dose CVVHDF for ICU-Related Acute Renal Failure

Ashita J. Tolwani,[*] Ruth C. Campbell,[*] Brenda S. Stofan,[*] K. Robin Lai,[†] Robert A. Oster,[*] and Keith M. Wille[*]

Departments of [*]Medicine and [†]Emergency Medicine, University of Alabama at Birmingham, Birmingham, Alabama

Medial and Surgical Units at UAB

Acute Kidney Injury: Volume overload, Oliguria, BUN>80, K>6.5, increase in Cr >2.5 or sustained increase in Cr>1 over baseline

200 patients randomized to high (35ml/kg/hr) versus low (20 ml/kg/hr) dose

Continuous Renal Replacement Therapy

Primary outcome:

Survival to ICU discharge or to day 30

No difference in mortality high vs low intensity RRT

J Am Soc Nephrol. 2008 Jun; 19(6): 1233–1238

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

ICU patients with AKI

1508 patients randomized to high (40 ml/kg/hr) versus low (25 ml/kg/hr) dose

The two study groups had similar baseline characteristics and received the study treatment for an average of 6.3 and 5.9 days, respectively (P=0.35).

At 90 days after randomization, 322 deaths had occurred in the higher-intensity group and 332 deaths in the lower-intensity group, for a mortality of 44.7% in each group (odds ratio, 1.00; 95% confidence interval [CI], 0.81 to 1.23; P=0.99).

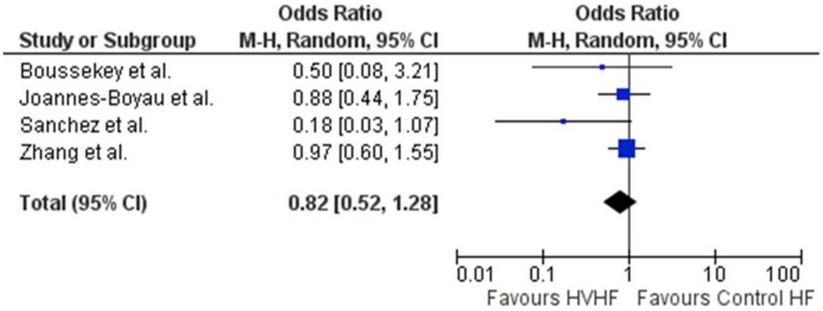
No difference in renal recovery

RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361:1627–1638

High Volume HemoFiltration and AKI

HVHF: ultrafiltration of more than > 35 ml/kg/hour

- Meta-analysis of four trials, including 470 total participants
- Insufficient evidence exists of a therapeutic benefit for routine use of HVHF for septic AKI



Study or Subgroup	Odds Ratio M-H, Random, 95% CI
Boussekey et al.	0.50 [0.08, 3.21]
Joannes-Boyau et al.	0.88 [0.44, 1.75]
Sanchez et al.	0.18 [0.03, 1.07]
Zhang et al.	0.97 [0.60, 1.55]
Total (95% CI)	**0.82 [0.52, 1.28]**

Forest plot for odds of 28-day mortality

Clark E, Critical Care 2014 18:R7

High Volume HemoFiltration and Sepsis

- IVOIRE study RCT 140 ICU patients*
  - no evidence that HVHF at 70 mL/kg/h, when compared to 35 mL/kg/h, leads to a reduction of 28-day mortality in sepsis AKI

*Joannes-Boyau O. Intensive Care Med 2013;39(9):1535-46

Summary Slide

- ARF/AKI in the ICU
  - Incidence of ARF in ICU ~ 6%,
  - 73% of these pts requiring RRT
  - In-hospital mortality still remains ~50%
- When to initiate RRT in ARF/AKI
  - Earlier may be better
- Does Modality matter?
  - CRRT is no better than IHD
- Does dose matter?
  - Less is the same as More

Board Question 1

A 24-yr-old male his legs pinned under a pile of rubble following an earthquake. He is extricated after 12 h. He is found to have scant red urine, a CPK of 46,000 U/L and a serum creatinine of 1.9 mg/dl.

Which one of the following treatments would have decreased the risk for AKI in this patient?

A. Intravenous crystalloid, initiated before extraction
B. Mannitol
C. Dopamine
D. Furosemide
E. N-acetyl-cysteine

Board Answer 1

A 24-yr-old male his legs pinned under a pile of rubble following an earthquake. He is extricated after 12 h. He is found to have scant red urine, a CPK of 46,000 U/L and a serum creatinine of 1.9 mg/dl.

Which one of the following treatments would have decreased the risk for AKI in this patient?

A. Intravenous crystalloid, initiated before extraction

- Urinary alkalinization may increase the solubility of heme proteins within the tubule.
- The use of mannitol is no better volume than expansion with saline.
- No benefit for dopamine, furosemide, or N-acetylcysteine in this setting.

Board Question 2

A 74-yr-old male with diabetes, congestive heart failure, and creatinine 2.1 mg/dl is admitted with a non–STEMI and is scheduled for a coronary angiography. Which one of the following would be associated with the least reduction in the risk for contrast-induced nephropathy?

A. A 250-ml infusion of isotonic sodium bicarbonate over 1 h before angiography followed by 75 ml/h for 6 h post angiography

B. A continuous infusion of isotonic sodium chloride at 75 ml/h for 12 h prior to angiography continuing for 12-h post angiography

C. A 250-ml infusion of isotonic sodium chloride over 1 h before angiography followed by a continuous infusion of 75 ml/h for 6 h post angiography

D. A continuous infusion of isotonic sodium bicarbonate at 75 ml/h for 4 h post angiography

E. A continuous infusion of isotonic sodium bicarbonate at 75 ml/h for 6 hours prior to angiography continuing for 6-h post angiography

Board Answer 2

A 74-yr-old male with diabetes, congestive heart failure, and creatinine 2.1 mg/dl is admitted with a non–STEMI and is scheduled for a coronary angiography. Which one of the following would be associated with the least reduction in the risk for contrast-induced nephropathy?

D. A continuous infusion of isotonic sodium bicarbonate at 75 ml/h for 4 h post angiography

- **Prevention of CIN**
- low-osmolar contrast media better than high-osmolar
- IV fluids better than oral hydration prior to procedure
- N-acetylcysteine Unclear benefit but low-risk profile and low cost
- $NaHCO_3$ Unclear benefit over saline
- Hemodialysis insufficient evidence

Board Question 3

Which One Renal Replacement method has the highest probability of in hospital survival?

A. Intermittent hemodialysis
B. CVVHDF
C. Sustained Low-Efficiency Dialysis
D. CVVH
E. All are equal

Board Answer 3

Which One Renal Replacement method has the highest probability of in hospital survival?

A. Intermittent hemodialysis
B. CVVHDF
C. Sustained Low-Efficiency Dialysis
D. CVVH
E. All are equal

Survival does not depend on modality of renal replacement in AKI with the exception of peritoneal dialysis (shown to be inferior)

Board Question 4

In CVVHDF which of the following is present?

A. Convection
B. Diffusion
C. Dialysate
D. Replacement Solution
E. All of the above

Board Answer 4

In CVVHDF which of the following is present?

A. Convection
B. Diffusion
C. Dialysate
D. Replacement Solution
E. All of the above

CVVHDF is Continuous Veno Venous HemoDia Filtration which is the combination of continuous hemofiltration (convection) and continuous dialysis (diffusion). Hemofiltration uses a replacement soultion while dialysis uses a dialysate.

Board Question 5

A 34-yr-old man develops severe oliguric AKI after thoracotomy. He has no evidence of sepsis. His CVP is 12 mmHh. Which is the best strategy for treatment?

A. Continuous venovenous hemofiltration with an effluent flow rate of 60 ml/kg per h.

B. Continuous venovenous hemodiafiltration with an effluent flow rate of 40 ml/kg per h.

C. Continuous venovenous hemofiltration with an effluent flow rate of 20 ml/kg per h.

D. Intravenous Furosemide 20mg/hr

E. Intravenous normal saline 75cc/hr

Board Answer 5

C. Continuous venovenous hemofiltration with an effluent flow rate of 20 ml/kg per h.

The data does not support the use of high dose (effluent flow rate of 60 or 40 ml/kg per h) in Continuous Renal Replacement. A lower dose is more cost effective.

With regard to modality there is no survival difference between CVVH and CVVHDF

Intravenous Furosemide 20mg/hr would not allow for solute clearance

Intravenous saline at 75cc/hr would likely not have an effect in this case.

References

- Palevsky PM, Murray PT: Acute kidney injury and critical care nephrology. NephSAP 5: 91–94, 2006
- Murray PT, Palevsky PM: Acute kidney injury and critical care nephrology. NephSAP 6: 303–305, 2007
- Vinsonneau et al. Lancet 2006; 368: 379-85
- Luyckx VA Semin Dial. 2004;17(1):30-6.

Conflict of Interest Disclosure Slide

- I have no financial relationships with commercial entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients relevant to the content I am presenting.

Acid-base Disorders; ABG's

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Overview

- Acid-Base Disorders
- Interpretation
- Anion Gap
- The Delta Ratio
- Urinary Anion Gap
- Osmolar Gap

Acid Base

The maintenance of a normal pH in the face of the 70,000,000 nmol of hydrogen ion generated daily depends on…

buffers
on the mechanisms for eliminating CO_2 through the lungs
the ability to eliminate acid in the urine.

Metabolic Alkalosis

- Metabolic alkalosis is a common disorder.
- Alkalosis is more likely in those who require nasogastric feeding compared with oral feeding.
- An inadequate metabolic response to chronic hypercapnia has been associated with increased mortality.

Initiation of Metabolic Alkalosis

Gain of alkali

Exogenous source (IV $NaHCO_3$ infusion, citrate in transfused blood pheresis or renal replacement)

Endogenous source (metabolism of ketoanions to produce bicarbonate)

Loss of H+

Kidneys (diuretics)

Gut (vomiting, Gastric suction)

Maintenance of Metabolic Alkalosis

Chloride depletion

Loss of gastric acid and diuretic use account for 90% of clinical cases of metabolic alkalosis

Loop / Thiazide Diuretics (Urinary chloride losses are greater than Urine bicarbonate losses). Seen only in volume depleted (high aldosterone) patients with low dietary chloride intake ('salt restricted' diet)

Potassium depletion

Bicarbonate reabsorption in both the proximal and distal tubules is increased in the presence of potassium depletion.

Primary hyperaldosteronism

Cushing’s syndrome – high dose corticosteroids

Urinary Chloride in Metabolic Alkalosis

If the cause is not apparent then Urine Cl can be helpful

Urine Cl- < 10 mmol/l

Volume depletion (increased proximal tubular reabsorption of HCO_3)

Responsive to IV NaCl (replaces chloride and volume)

Cause: Vomiting (90% of cases), Prior thiazide diuretic use

Urine Cl- > 20 mmol/l

Volume expansion and hypokalaemia

Not responsive to IV NaCl

Cause: Excess aldosterone, severe K+ deficiency, Current diuretic therapy

Metabolic Alkalosis

Compensation

Hypoventilation causes a compensatory rise in arterial pCO_2

Magnitude of the response has generally been found to be quite variable.

Expected $pCO_2 = 0.7\ [HCO_3] + 20\ mmHg \pm 5$

Correction

Treat underlying disorder

Repletion of chloride, potassium and volume will improve renal bicarbonate excretion

Major Effects of Metabolic Alkalosis

Respiratory Effects

Respiratory depression via both central and peripheral chemoreceptors.

Cardiovascular Effects

Decreases oxygen delivery to the tissues by exerting a vasoconstrictor effect and by impairing hemoglobin’s ability to release oxygen.

Alkalosis-induced tissue hypoxemia can adversely affect cerebral, coronary, and peripheral circulation.

An inadequate metabolic response to chronic hypercapnia has been associated with increased mortality.

Acetazolamide

- Carbonic anhydrase inhibitors hinder renal acidification causing the kidney to partially correct the metabolic alkalosis.
- Only rarely does the plasma HCO_3 concentration return to normal.

- A potential problem associated with use of carbonic anhydrase inhibitors in patients with lung disease is a worsening of hypercapnia.
- Carbonic anhydrase inhibition can prevent red cell uptake of CO_2 in peripheral tissues and can prevent CO_2 release in the lung.

Metabolic Acidosis

- Metabolic acidosis is a disorder that reduces the extracellular bicarbonate concentration.
- Accumulation of excess acids that consume bicarbonate
    - Generates a high anion gap (AG) acidosis because the excess acids contribute an organic anion to the circulation as well as a hydrogen ion.
- Gastrointestinal or renal loss of bicarbonate salts.
    - Non gap acidosis.

Metabolic Acidosis

- The kidney's role in regulating acid-base balance includes
  - Reclamation of filtered HCO_3 and
  - Regeneration of HCO_3 consumed by net acid production.
- Quantitatively, the most important urinary buffer is the NH_3/NH_4^+ (Ammonia/Ammonium) system. $H^+ + NH_3 \rightarrow NH_4^+$
- The rate of NH_3 production and excretion can be varied according to physiologic needs.
- Under normal circumstances, urine excretion of NH_4^+ accounts for more than half of the net acid excreted per day.
- Acidosis and hypokalemia stimulate NH_4^+ excretion.
- Alkalosis and hyperkalemia diminish NH_4^+ excretion.

Non gap / Hyperchloremic Metabolic Acidosis

Renal Causes

Renal tubular acidosis
Carbonic anhydrase inhibitors

GI Causes

Severe diarrhea
Uretero-enterostomy or Obstructed ileal conduit
Drainage of pancreatic or biliary secretions
Small bowel fistula

Other Causes

Recovery from ketoacidosis
Addition of HCl, NH_4Cl

Urinary Anion Gap

- Useful for Non gap (or hyperchloraemic) acidosis that is not obvious
- Only Na+, K+ and Cl- are commonly measured in urine so the other charged species are the unmeasured anions (UA) and cations (UC).
- Urinary Anion Gap = (UA - UC) = [Na+]+ [K+] - [Cl-]
- Urinary Anion Gap (UAG) provides a rough index of urinary ammonium (NH_4^+) excretion.
- With normal kidney function and acidosis, urine NH_4Cl should increase driving the UAG negative.
- A negative UAG = GI loss of bicarbonate (diarrhea) "neGUTive"
- A positive UAG = impaired renal distal acidification (RTA).

Anion Gap

- Anions associated with:
    - endogenous organic acidosis (lactate, beta-hydroxybutyrate, and acetoacetate)
    - Exogenous poisons (formate, glycolate, salicylate)
    - Renal failure (sulfate, phosphate, and other anions)
- Negative charges on plasma albumin are a large component of the unmeasured anions that make up the calculated AG.
- Hypoalbuminemia will lead to an underestimate of the size of the AG and potentially to the failure to recognize a clinically important high AG acidosis.
- A "corrected anion gap" avoids this problem: For every 1 g/dl decrease in serum albumin below 4.4 g/dl, 2.5 mEq/L is added to the calculated AG.

Anion Gap

An elevated Anion Gap always strongly suggests a Metabolic Acidosis

AG 20-30: high chance of metabolic acidosis
AG > 30: metabolic acidosis is certainly present

Delta/Delta

Delta Ratio Assessment Guidelines in patients with a metabolic acidosis

< 0.4	Hyperchloremic non gap acidosis
0.4 - 0.8	Combined high AG and non gap acidosis
1 to 2	Typical pattern in high AG metabolic acidosis
> 2	Either a co-existing Metabolic Alkalosis or a co-existing Chronic Respiratory Acidosis

Delta/Delta

Increase in Anion Gap / Decrease in bicarbonate

If one molecule of metabolic acid (HA) is added to the ECF and dissociates, the one H+ released will be buffered by one molecule of HCO_3^- to produce CO_2 and H_2O.

The net effect will be an increase in unmeasured anions by the one acid anion A- (ie anion gap increases by one) and a decrease in the bicarbonate by one.

Significant intracellular buffering with extracellular retention of the unmeasured acid anion (A-) will cause the value of the delta ratio to be greater than one in a high AG metabolic acidosis.

Delta/Delta example

“Normal” AG 10 Normal HCO_3 24

Case 1
Anion gap 20 HCO_3 17
Delta AG/ Delta HCO_3 = 20-10/24-17 = 1.42 -> uncomplicated high-AG acidosis

Case 2
Anion gap 20 HCO_3 12
Delta AG/ Delta HCO_3 = 20-10/24-12 = 0.08 -> less HCO_3 than expected
High AG acidosis with additional nongap acidosis

Case 3
Anion gap 20 HCO_3 20
Delta AG/ Delta HCO_3 = 20-10/24-20 = 2.5 -> more HCO_3 than expected
High AG acidosis with additional metabolic alkalosis or additional compensated respiratory acidosis

Delta/Delta

Increase in Anion Gap / Decrease in bicarbonate

< 0.4
Hyperchloraemic nongap acidosis

0.4 - 0.8
Combined High AG and nongap acidosis
acidosis associated with renal failure Delta/Delta < 1

Less HCO_3 present than expected by increase in AG

1 to 2
Usual for uncomplicated high-AG acidosis
Lactic acidosis, DKA

> 2
Pre-existing elevated HCO_3 level so consider:
concurrent metabolic alkalosis, or
pre-existing compensated respiratory acidosis

More HCO_3 present than expected by increase in AG

Osmolar gap

The osmolar gap is the difference between the measured osmolality and the calculated osmolarity.

Measured Osmolality is measured in the lab via an osmometer

Calculated Osmolarity = (2 x [Na+]) + glucose/18 + BUN/2.8 + ethanol/4.6

Osmolar gap

Screening test for detecting abnormal low molecular weight solutes

methanol	(Osm gap + high AG)
ethylene glycol	(Osm gap + high AG)
ethanol	(Osm gap + normal AG)
acetone	(Osm gap + normal AG)
isopropyl ethanol	(Osm gap + normal AG)
propylene glycol	(Osm gap + high AG, vehicle in Ativan IV)

osmolar gap > 10 mOsm/l is often stated to be abnormal
osmolar gap≥ 25 is suggestive of methanol or ethylene glycol ingestion

Major Effects of Metabolic Acidosis

Respiratory Effects

Hyperventilation - compensatory response
Shift of oxyhaemoglobin dissociation curve to the right
Decreased 2,3 DPG levels in red cells (shifting back to the left)

Cardiovascular Effects

Depression of myocardial contractility
Sympathetic overactivity
Resistance to the effects of catecholamines
Peripheral arteriolar vasodilatation

Respiratory Acidosis

An adult at rest produces 200mls of CO_2 per minute

Increased production of CO_2 leads to a respiratory acidosis if ventilation remains constant.

Increases in pCO_2 very promptly results in a large increase in ventilation maintaining the at pCO_2 40 mmHg.

Respiratory Acidosis

Inadequate Alveolar Ventilation (most common)
- Central Respiratory Depression & Other CNS Problems
- Inadequate mechanical ventilation
- Nerve or Muscle Disorders
- Lung or Chest Wall Defects
- Airway Disorders (obstruction)

Over-production of Carbon Dioxide
- Hypercatabolism (Malignant Hyperthermia)

Increased Intake of Carbon Dioxide
- Rebreathing of CO2-containing expired gas
- Insufflation of CO2 into body cavity (laparoscopic surgery)

Respiratory Acidosis

Hypercapnea

- Stimulation of ventilation via both central and peripheral chemoreceptors
- Cerebral vasodilation increasing cerebral blood flow and intracranial pressure
- Central depression at very high levels of pCO2
- Stimulation of the sympathetic nervous system resulting in tachycardia, peripheral vasoconstriction and sweating
- Peripheral vasodilation by direct effect on vessels

Respiratory Acidosis

The compensatory response to an acute respiratory acidosis is limited to buffering rapidly inside red blood cells via carbonic anhydrase and hemoglobin

$CO_2 + H_2O <-> H_2CO_3 <-> H+ + HCO_3-$

With continuation of the acidosis, the kidneys respond by retaining bicarbonate.

The renal response begins by 6 - 12 hours and is maximal at 3 - 4 days.

- Increased HCO_3 production
- Increased NH_3 production to 'buffer' the H+ to increase urinary excretion of NH_4Cl

The pCO_2 quickly returns to normal with restoration of adequate alveolar ventilation

Respiratory Acidosis

The pCO_2 quickly returns to normal with restoration of adequate alveolar ventilation

The correction of the elevated bicarbonate (renal compensation) associated with chronic respiratory acidosis may not be rapid.

Return of plasma bicarbonate to normal requires renal excretion of the excess bicarbonate.

Certain abnormal conditions the excretion is impaired and the bicarbonate level remains elevated.

The persistence of elevated bicarbonate despite resolution of the chronic respiratory acidosis is referred to by some as 'post-hypercapnic alkalosis'

Respiratory Alkalosis

A respiratory alkalosis is a primary acid-base disorder in which arterial pCO2 falls to a level lower than expected

A respiratory alkalosis is due to increased alveolar ventilation
The low arterial pCO2 will be sensed by the central and peripheral chemoreceptors and the hyperventilation will be inhibited unless the patient's ventilation is controlled

Consequences:

- decreased cerebral blood flow
- decrease in myocardial contractility
- shift of the oxygen dissociation curve to the left

Respiratory Alkalosis

Central Causes

Head Injury, Stroke
Anxiety, Pain, fear, Drugs (salicylate intoxication)
progesterone during pregnancy, cytokines during sepsis

Hypoxemia

peripheral chemoreceptors stimulate respiration

Pulmonary Causes (act via intrapulmonary receptors)

Pneumonia, Asthma, Pulmonary Embolism, Pulmonary edema

Iatrogenic

Excessive controlled ventilation

Respiratory Alkalosis

Acute

The buffering is by intracellular proteins
  slight decrease in HCO_3-
Renal compensation has insufficient time to respond
The lower limit of 'compensation' is 18mmol/l

Chronic

Renal loss of bicarbonate causes a further fall in plasma bicarbonate
This maximal response takes 2 to 3 days to reach.
The limit of compensation is a [HCO_3-] of 12 to 15 mmol/l.

Respiratory Alkalosis

A patient cannot have both a respiratory alkalosis and a respiratory acidosis

Hyperventilation is used to acutely decrease intracranial pressure as the onset is rapid.

The effect on cerebral blood flow is time-limited as equilibration of bicarbonate across the blood-brain barrier occurs over 4 to 6 hours and cerebral blood flow and intracranial pressure return towards normal

Acid-Base Interpretation

1. Clinical stem (vomiting/ nasogastric suction / diarrhea)
2. pH: <7.40 Acidemia or >7.40 Alkalemia
   pH=7.40 can occur with mixed acid base disorders
3. Pattern of HCO_3 and pCO_2 (primary disorder)
4. Is compensation appropriate?
5. Is Anion Gap (AG) present?
6. If AG then Delta/Delta and Osmolar Gap
7. Hints in other investigations (urine ketones)

Rules for Acid-Base Disorders

Acute Respiratory Acidosis
Expected HCO_3= 24 +1[(Actual pCO_2-40)/10]

Chronic Respiratory Acidosis
Expected HCO_3 = 24 +4[(Actual pCO_2-40)/10]

Acute Respiratory Alkalosis
Expected HCO_3 = 24 -2[(40-Actual pCO_2)/10]

Chronic Respiratory Alkalosis
Expected HCO_3 = 24 -5[(40-Actual pCO_2)/10]

Metabolic Alkalosis
Expected pCO2 = 0.7 [HCO3] + 20

Metabolic Acidosis
Expected pCO2 = 1.5 [HCO3] + 8

Hints

High anion gap
- Metabolic acidosis

Hypokalaemia and/or hypochloraemia
- Metabolic alkalosis

Hyperchloraemia
- Normal anion gap acidosis

Elevated creatinine and urea
- Uremia acidosis or prerenal renal failure

Hyperglycaemia
- DKA or hyperosmolar non-ketotic syndrome

Summary Slide

1. Clinical stem
2. pH
3. Pattern of HCO_3 and pCO_2 (primary disorder)
4. Is compensation appropriate?
5. Is Anion Gap (AG) present?
6. If AG then Delta/Delta and Osmolar Gap
7. Hints in other investigations

Respiratory Acidosis and Alkalosis cannot occur together
More than one metabolic acid-base disorder can be present at one time
Urine AG for Non gap acidosis [NeGUTive]
Urinary Chloride in Metabolic Alkalosis

Board Question 1

A 58 year old diabetic woman on insulin was found down nearly unresponsive. Reported to be sick for several days. Past history of CHF. Medications included insulin, digoxin and a thiazide diuretic.

Lytes: K+ 2.8, HCO_3 18, glucose 70, anion gap 31
Arterial Blood Gases pH 7.40, pCO_2 34, pO_2 84

Q: Acid base disorder present is:
A: No acid-base disorder is present
B: High Anion Gap Metabolic Acidosis
C: High Anion Gap Metabolic Acidosis and respiratory alkalosis
D: High Anion Gap Metabolic Acidosis and metabolic alkalosis
E: High Anion Gap Metabolic Acidosis, non gap acidosis and metabolic alkalosis

Board Answer 1

HCO_3 18, anion gap 31, pH 7.40, pCO_2 34, diabetic on thiazide

Q: Acid base disorder present is:

D: High Anion Gap Metabolic Acidosis and metabolic alkalosis

1. Clinical stem (diabetes, obtundation)
2. pH: 7.40 can occur with mixed acid base disorders
3. Pattern of HCO_3 and pCO_2 (primary metabolic acidosis AG+)
4. Is compensation appropriate? expected pCO2 is ((1.5 x 18) + 8) = 35
5. Is Anion Gap (AG) present? yes
6. Delta/Delta and Osmolar Gap
   Delta/Delta = (31-10)/(24-18) = 3.5 ∴ more HCO_3 than expected = metabolic alkalosis probably from thiazide
   Not enough information for Osmolar Gap
7. Hints in other investigations (urine ketones, serum Osm)

Board Question 2

A 35 yr old healthy female presented with confusion and abdominal pain 8 hours following exercise. RR 22/min.

There was no evidence of intoxication. EtOH=0

Lytes: Na+ 135, K+ 3.7, Cl 109, BUN 12, Glu 106, HCO_3 23,

pH 7.42, pCO_2 35, pO_2 138

Serum osmolality 319 mOsm/kg H_2O

Q: Acid base disorder present is:

A: No acid-base disorder is present

B: High Anion Gap Metabolic Acidosis

C: High Anion Gap Metabolic Acidosis and respiratory alkalosis

D: High Anion Gap Metabolic Acidosis and metabolic alkalosis

E: High Anion Gap Metabolic Acidosis, non gap acidosis and metabolic alkalosis

Board Answer 2

Q: Acid base disorder present is:

A: No acid-base disorder is present

1. Clinical stem (confusion ? intoxication)
2. pH: 7.42 can occur with mixed acid base disorders or no disorder
3. Pattern of HCO_3 and pCO_2 (not abnormal)
4. Is compensation appropriate? No compensation
5. Is Anion Gap (AG) present? AG= 3
6. Osmolar Gap

Calculated osmolarity = (2 x [Na+]) + glucose/18 + BUN/2.8 + ethanol/4.6

Calculated osmolarity = (2 x [135]) + 106/18 + 12/2.8 + 0/4.6 = 280

Osm Gap = 319-280 = 39 indicating

Methanol levels later returned at 30g/dl. Anion gap is absent as patient presented before methanol was metabolized to formaldehyde & formic acid (unmeasured anons)

Board Question 3

An 82 year old woman presented with profound weakness and areflexia. Her PO intake had been poor for a few days.

Lytes: Na^+ 146, K^+ 2.0, Cl^- 87, HCO_3 44, urine chloride 78 mmols/l.

pH 7.58, pCO_2 49, pO_2 - not given

Q: Acid base disorder present is:

A: No acid-base disorder is present

B: Respiratory alkalosis

C: High Anion Gap Metabolic Acidosis and respiratory alkalosis

D: Chloride responsive Metabolic alkalosis

E: Chloride resistant Metabolic alkalosis

Board Answer 3

Elderly woman with profound weakness and areflexia

Lytes: Na^+ 146, K^+ 2.0, Cl^- 87, HCO_3 44, urine chloride 78 mmols/l.

pH 7.58, pCO2 49, pO2 - not given

Q: Acid base disorder present is:

E: Chloride resistant Metabolic alkalosis

1. Clinical stem (not helpful)
2. pH: 7.58 alkalemia
3. Pattern of HCO_3 and pCO_2 (primary metabolic alkalosis)
4. Is compensation appropriate? Expected pCO2 = 0.7 [HCO3] + 20 = 51 yes
5. Is Anion Gap (AG) present? AG= 15 borderline
6. Hints in other investigations (urine chloride >20)

Severe metabolic alkalosis with life-threatening hypokalaemia.

The high urinary chloride suggests a cause in the chloride resistant group (excess steroids or current diuretic use).

Board Question 4

A 73 year old man presented with acute on chronic CHF. Patient had vomiting for 5 days. Patient stopped taking his medications. He was tachypneic and uncomfortable on oxygen.

Lytes: Na 128, K 5.2, Cl 78, HCO_3 20, urea 50, creatinine 6, gluc 108

pH 7.57, pCO_2 22, pO_2 145

Q: Acid base disorder present is:

A: No acid-base disorder is present

B: Respiratory Alkalosis

C: High Anion Gap Metabolic Acidosis with non gap metabolic acidosis and Respiratory Alkalosis

D: Metabolic Alkalosis

E: Primary Respiratory Alkalosis with high anion gap Metabolic Acidosis and Metabolic Alkalosis

Board Answer 4

Q: Acid base disorder present is:

E: Primary Respiratory Alkalosis with high anion gap metabolic acidosis and metabolic alkalosis

1. Clinical stem (CHF lactic acidosis, vomiting metabolic alkalosis, tachypnea Respiratory alkalosis, renal failure high anion gap metabolic acidosis)
2. pH: 7.57 alkalemia
3. Pattern of HCO_3 and pCO_2 (primary respiratory alkalosis)
4. Is compensation appropriate? Expected HCO_3 = 24 -5[(40-Actual pCO_2)/10] = 15. Actual HCO_3 is 20 indicating metabolic alkalosis is present
5. Is Anion Gap (AG) present? AG= 30
6. Delta/Delta and Osmolar Gap

   Delta/Delta = (30-10)/(24-20) = 5 ∴ more HCO_3 than expected = metabolic alkalosis
7. Hints in other investigations (urine chloride >20)

Board Question 5

A 70 year old male patient had a cardiac arrest shortly following admission. Resuscitation included intubation and bag ventilation. Blood gas during code pH 6.85, pCO_2 82, pO_2 214, HCO_3 14, Anion gap 24, Lactate 12 mmol/l.

Q: Acid base disorder present is:

A: High Anion Gap Metabolic Acidosis with Respiratory Acidosis and Respiratory Alkalosis

B: High Anion Gap Metabolic Acidosis

C: High Anion Gap Metabolic Acidosis with Respiratory Acidosis

D: High Anion Gap Metabolic Acidosis with non gap metabolic acidosis and Respiratory Acidosis

E: High Anion Gap Metabolic Acidosis with non gap metabolic acidosis and Respiratory Alkalosis

Board Answer 5

Cardiac arrest. pH 6.85, pCO2 82, pO2 214, Anion gap 24, Lactate 12 mmol/l.

Q: Acid base disorder present is:

C: High Anion Gap Metabolic Acidosis with Respiratory Acidosis

1. Clinical stem (lactic acidosis HAGMA, poor ventilation Respiratory acidosis)
2. pH: 6.85 acidemia
3. Pattern of HCO_3 and pCO_2 (primary metabolic acidosis)
4. Is compensation appropriate? Expected pCO2 = 1.5 [14] + 8 = 29 Actual pCO_2 is 82 indicating Respiratory Acidosis is present
5. Is Anion Gap (AG) present? AG= 24
6. Delta/Delta and Osmolar Gap

   Delta/Delta = (24-10)/(24-14) = 1.4 ∴ HCO_3 as expected

References

- Gupta M, Wadhwa NK, Bukovsky R: Regional citrate anticoagulation for continuous venovenous hemodiafiltration using calcium-containing dialysate. Am J Kidney Dis 43: 67–73, 2004
- Sterns RH, Palmer BF. Nephrology Self-Assessment Program - Vol 5, No 1, January 2006
- 'Acid-base pHysiology' by Kerry Brandis -from http://www.AnaesthesiaMCQ.com
- Hoffman RS, Smilkstein MJ, Howland MA, Goldfrank LR. Osmol gaps revisited: normal values and limitations. J Toxicol Clin Toxicol. 1993;31(1):81-93.

Conflict of Interest Disclosure Slide

- I have no financial relationships with commercial entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients relevant to the content I am presenting.

Ventilator Associated Pneumonia

Brigham Board Review in Critical Care
2017

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Associate Hospital Epidemiologist, Brigham and Women's Hospital

Disclosures

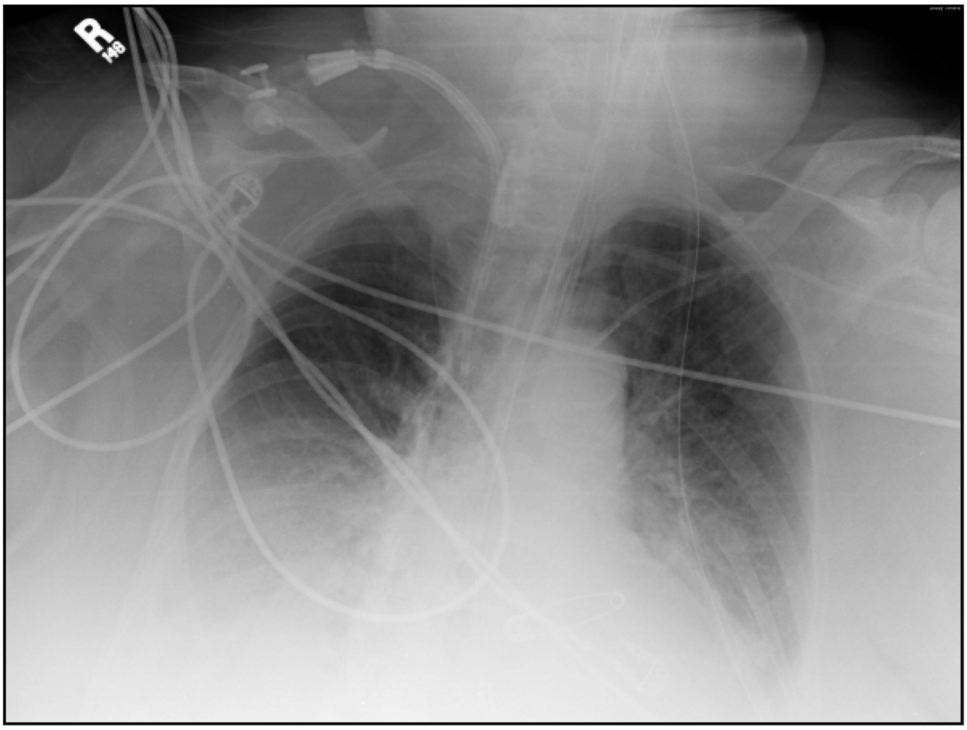
- Reports no commercial interest

Outline

- How accurate are clinical signs to diagnose pneumonia?
- What kind of imaging should we get?
- What pathogens are associated with VAP?
- What should we treat with?
- Do we need to get cultures?
- How long should we treat for?
- How can we improve outcomes for ventilated patients?

Case Study

- A 68 year old man is admitted to the medical intensive care unit with severe pancreatitis. A large bore catheter is placed for aggressive fluid resuscitation. A foley catheter is placed to monitor urine output. Pain is managed with a continuous infusion of opioids
- The patient develops progressive hypoxemia. A chest x-ray shows bilateral pulmonary infiltrates. The patient requires intubation
- The patient has daily fevers. On hospital day 4, the patient's nurse thinks he looks more drowsy than before and has more secretions.
- On exam, he opens eyes to voice but doesn't follow any commands. Temperature is 101.9, HR 118, BP 98/64. Vent settings are AC, PEEP 10cm H2O, FiO2 50%. JVP is difficult to visualize. Possible crackles in the bases. Marked abdominal distention. Bilateral lower extremity edema.
- Labs are notable for WBC count of 12.2, hct 32, plt 140, Na 130, creatinine 1.8, LFTs normal, INR 1.0.
- Urinalysis with 4-6 WBC/hpf
- Portable chest x-ray with edema +/- LLL infiltrate



"Diffuse patchy airspace disease right greater than left with obliteration of both hemi-diaphragms. Opacities possibly slightly increased since yesterday accounting for changes in patient position and inspiration. This could represent atelectasis, pneumonia, or effusion."

Does this patient have pneumonia?

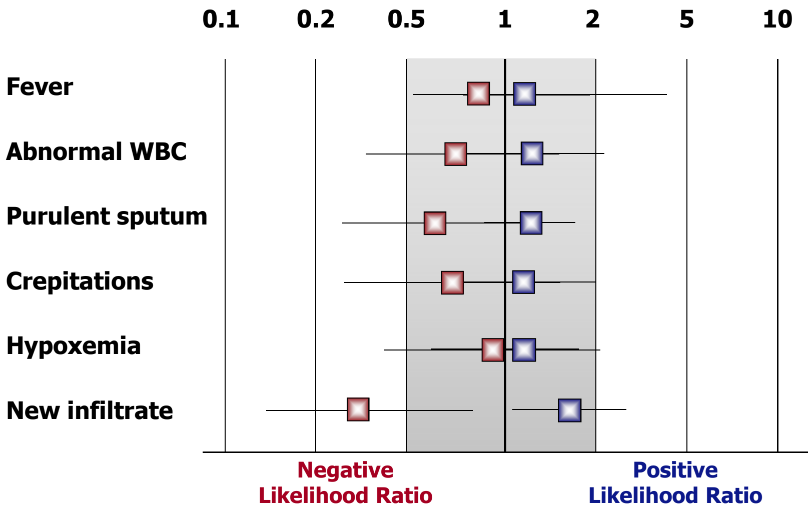
Would you start antibiotics?

Why is Pneumonia So Difficult to Diagnose?

- Many medical conditions in hospitalized patients present with the same clinical signs as pneumonia
  - Radiographic opacities
  - Fever
  - Abnormal white blood cell count
  - Impaired oxygenation
  - Increased pulmonary secretions

Accuracy of clinical signs for VAP

Relative to autopsy, systematic review, 14 studies, 655 pts



JAMA 2007; 297:1583

Sources of fever and infiltrates

- ARDS
- Diffuse alveolar damage
- Thromboembolic disease
- Hemorrhage
- Infarction
- Fibrosis
- Carcinoma
- Lymphoma
- Contusion

Tracheobronchitis
CLABSI
UTI
Drug fever

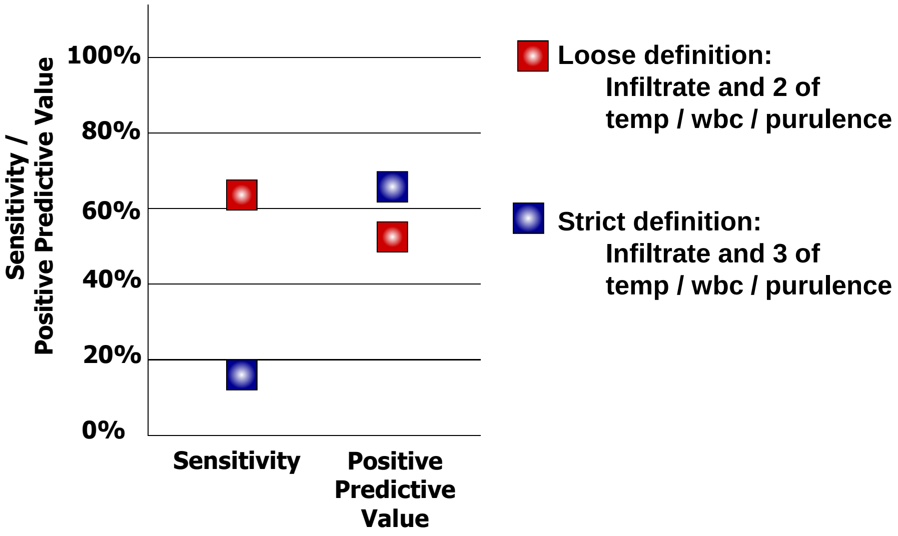
PLUS

Pulmonary edema
Atelectasis
Contusion
Fibrosis

Meduri, *Chest* 1994; 106:221-235
Petersen, *Scand J Infect Dis* 1999; 31:299-303

Accuracy of Clinical Diagnosis of VAP

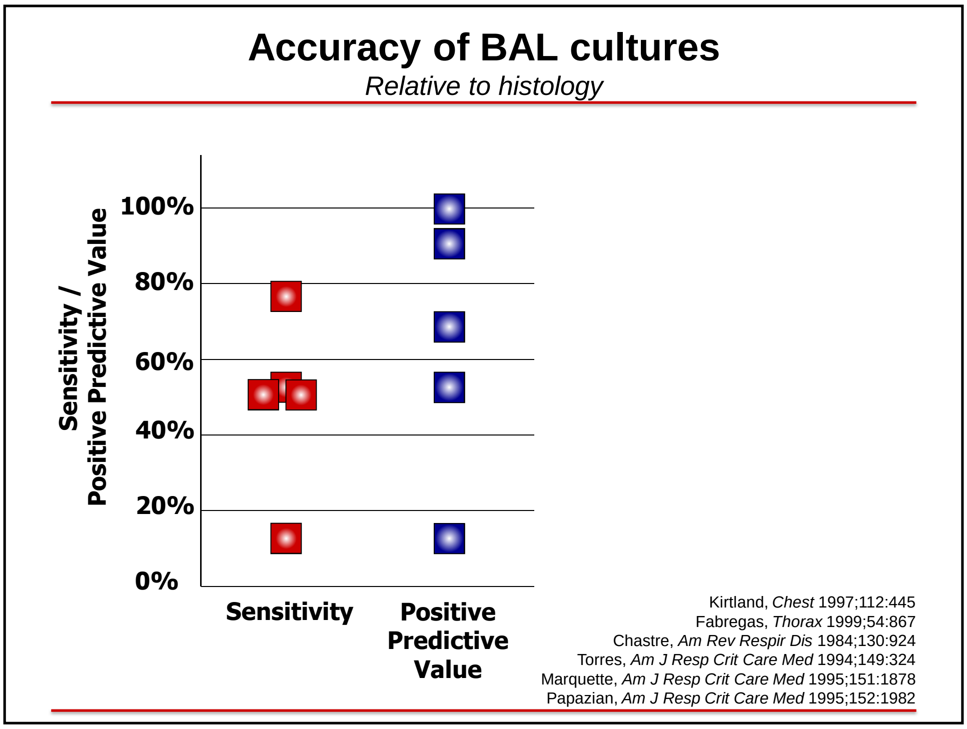
Relative to 253 autopsies



🟥 **Loose definition:**
Infiltrate and 2 of
temp / wbc / purulence

🟦 **Strict definition:**
Infiltrate and 3 of
temp / wbc / purulence

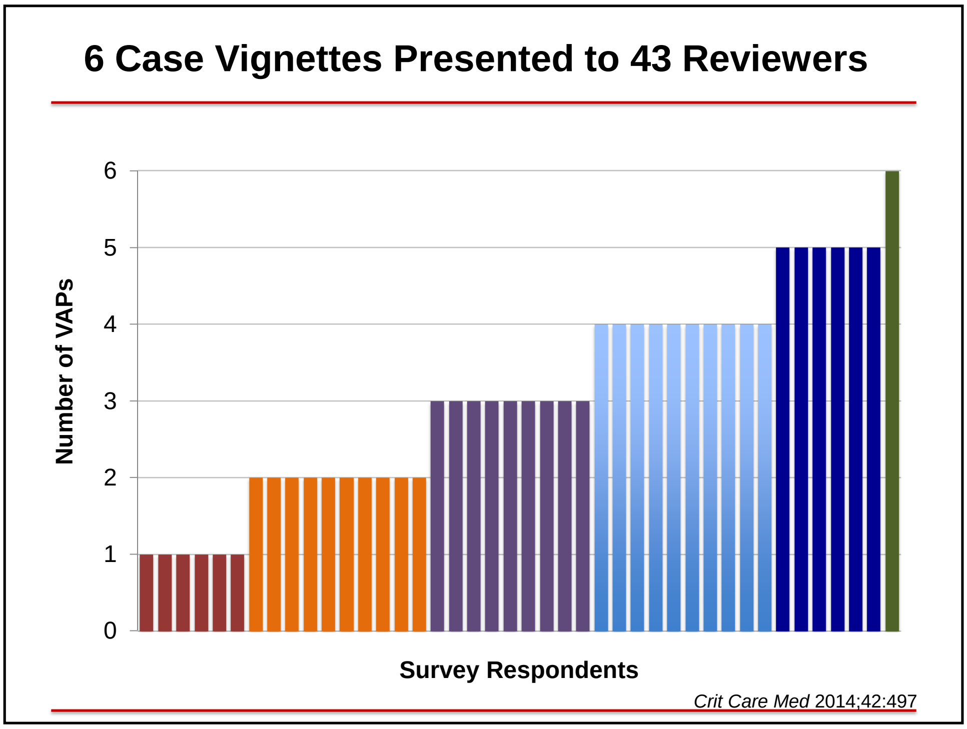
Tejerina et al., *J Critical Care* 2010;25:62



Accuracy of BAL cultures

Relative to histology

Kirtland, *Chest* 1997;112:445
Fabregas, *Thorax* 1999;54:867
Chastre, *Am Rev Respir Dis* 1984;130:924
Torres, *Am J Resp Crit Care Med* 1994;149:324
Marquette, *Am J Resp Crit Care Med* 1995;151:1878
Papazian, *Am J Resp Crit Care Med* 1995;152:1982



6 Case Vignettes Presented to 43 Reviewers

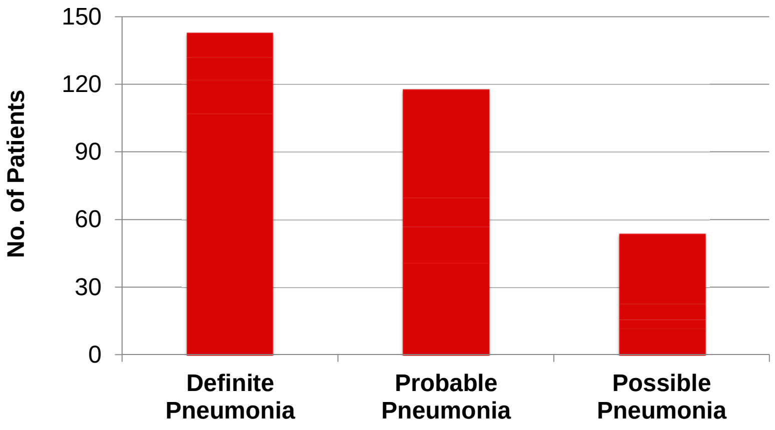
Crit Care Med 2014;42:497

Would further imaging help?

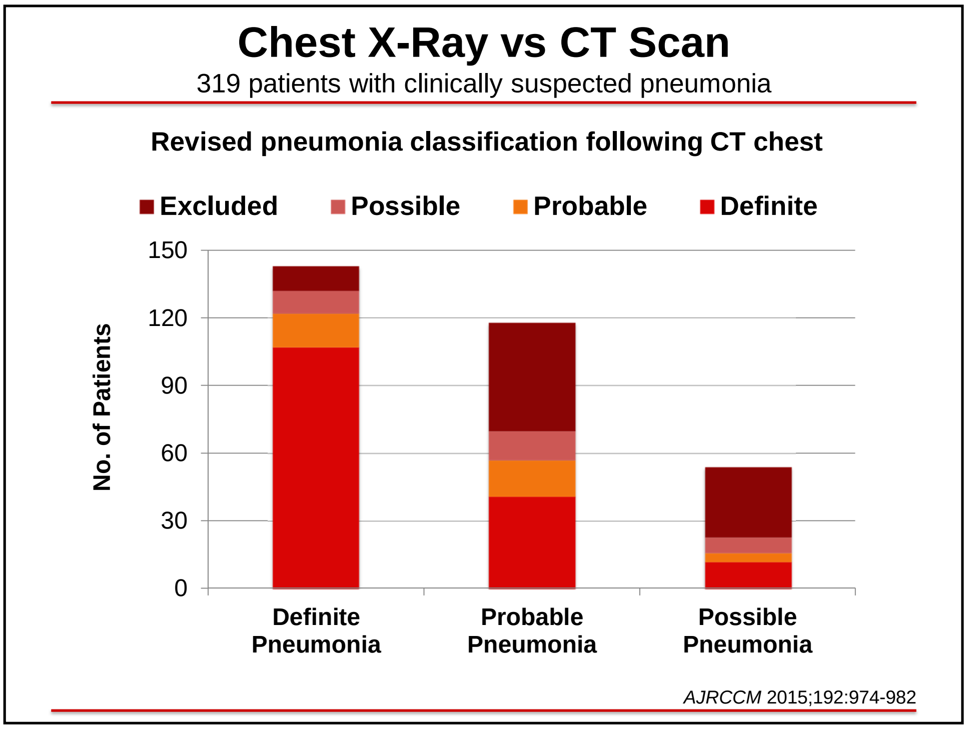
Chest X-Ray vs CT Scan

319 patients with clinically suspected pneumonia

Initial pneumonia classification following chest x-ray



AJRCCM 2015;192:974-982

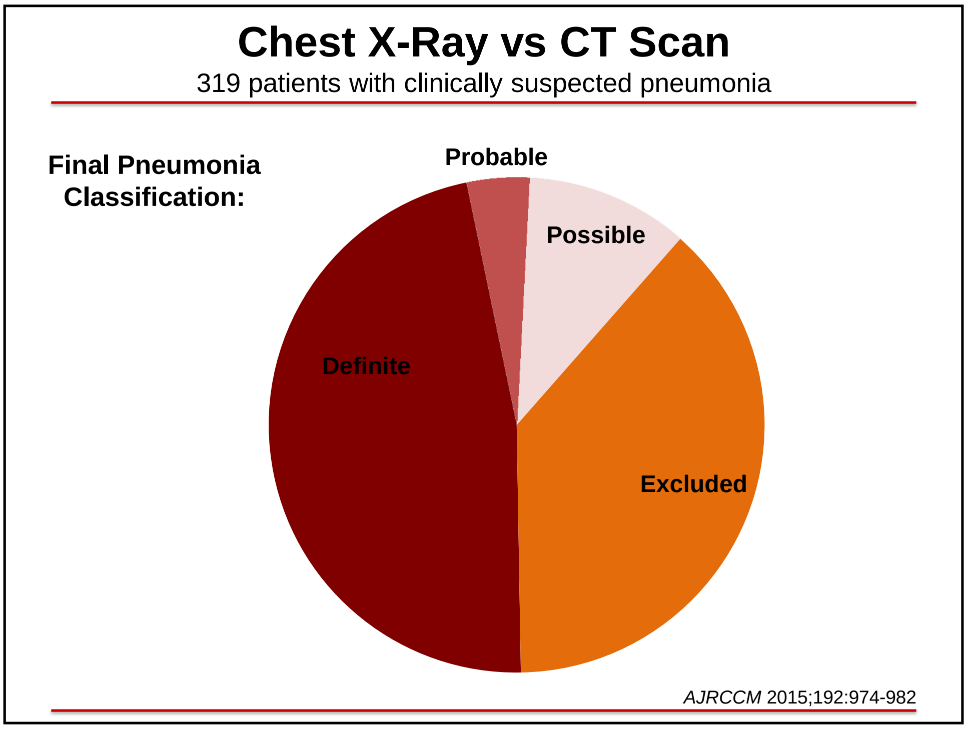


Chest X-Ray vs CT Scan

319 patients with clinically suspected pneumonia

Revised pneumonia classification following CT chest

AJRCCM 2015;192:974-982

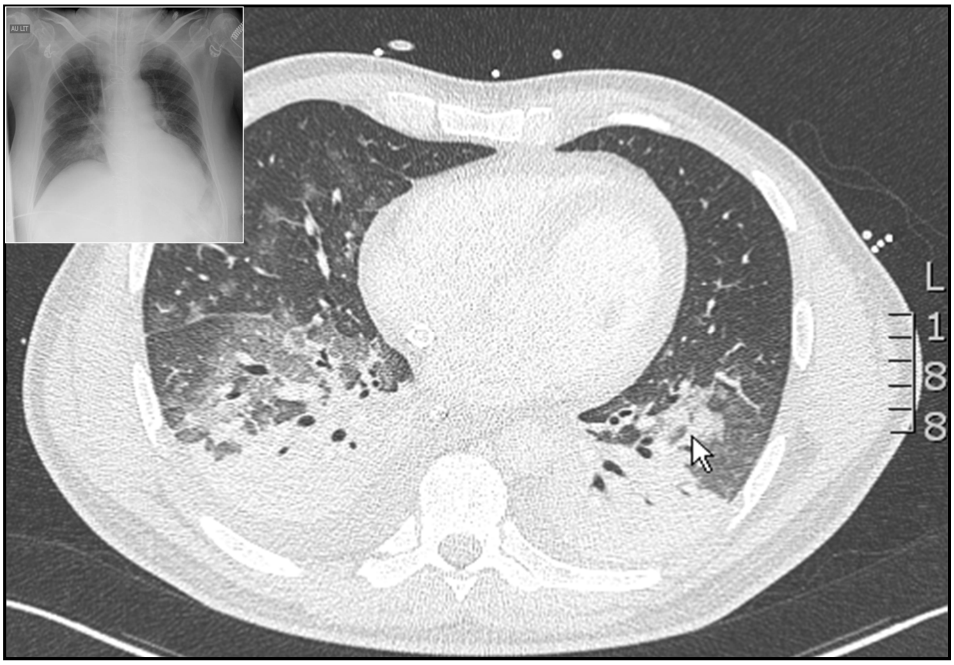


Chest X-Ray vs CT Scan

319 patients with clinically suspected pneumonia

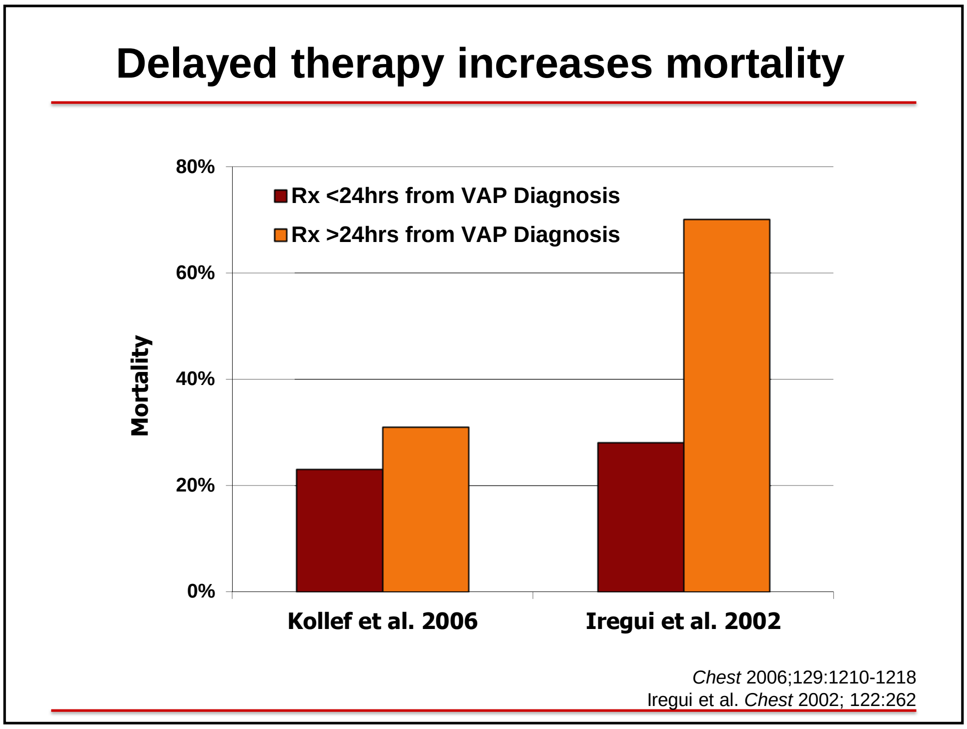
Final Pneumonia Classification:

AJRCCM 2015;192:974-982



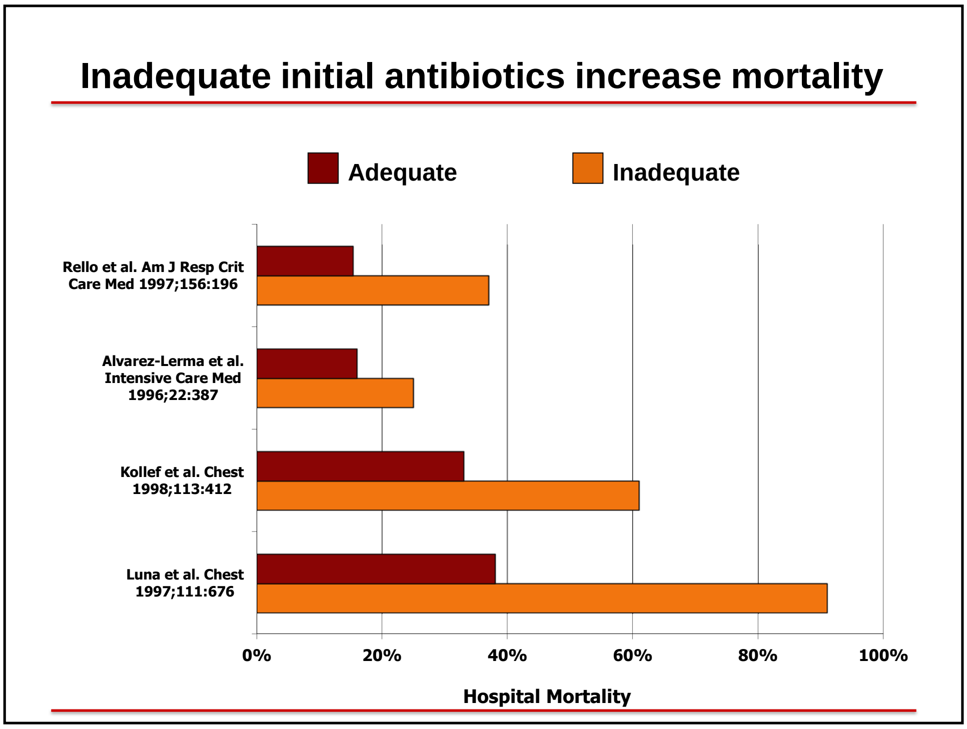
Intensive Care Med 2016;42:1159-63

Do we have to start antibiotics right away?



Delayed therapy increases mortality

Chest 2006;129:1210-1218
Iregui et al. *Chest* 2002; 122:262



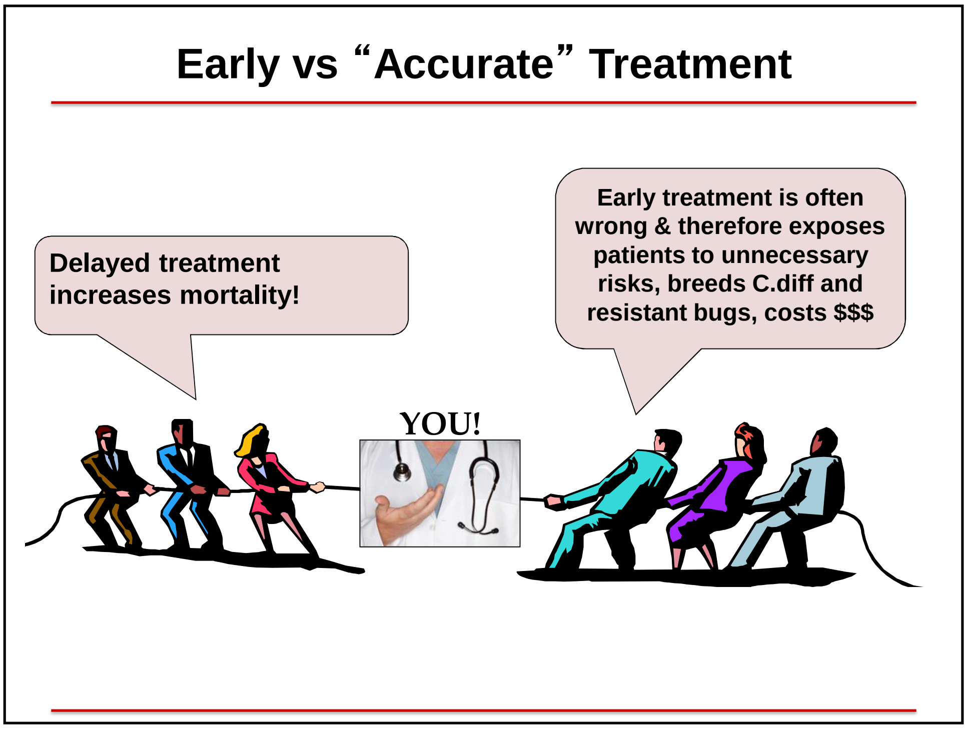
Inadequate initial antibiotics increase mortality

Overtreatment also risky…

- **Misdiagnosis**
  - 30-60% of patients started on abx for VAP do not have VAP
- ***Clostridium difficile***
  - ~8% of hospitalized patients on abx for >1 week get C.diff
- **Resistance**
  - Drug resistant organisms associated with higher mortality rates
- **Direct drug adverse effects**
  - Renal & hepatic toxicity, rash, cytopenias, drug fever
- **Expensive**

Clin Infect Dis 2007;45:1543-49
Clin Infect Dis 2009;48:568-76
Chest 1993;104:1230-5
Chest 2006;129:1210-1218

Early vs “Accurate” Treatment



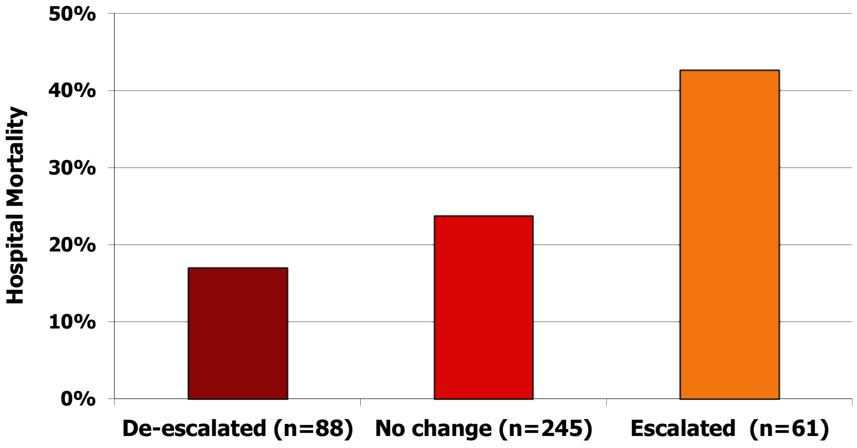
Delayed treatment increases mortality!

Early treatment is often wrong & therefore exposes patients to unnecessary risks, breeds C.diff and resistant bugs, costs $$$

Start early,
Re-evaluate frequently,
Stop judiciously

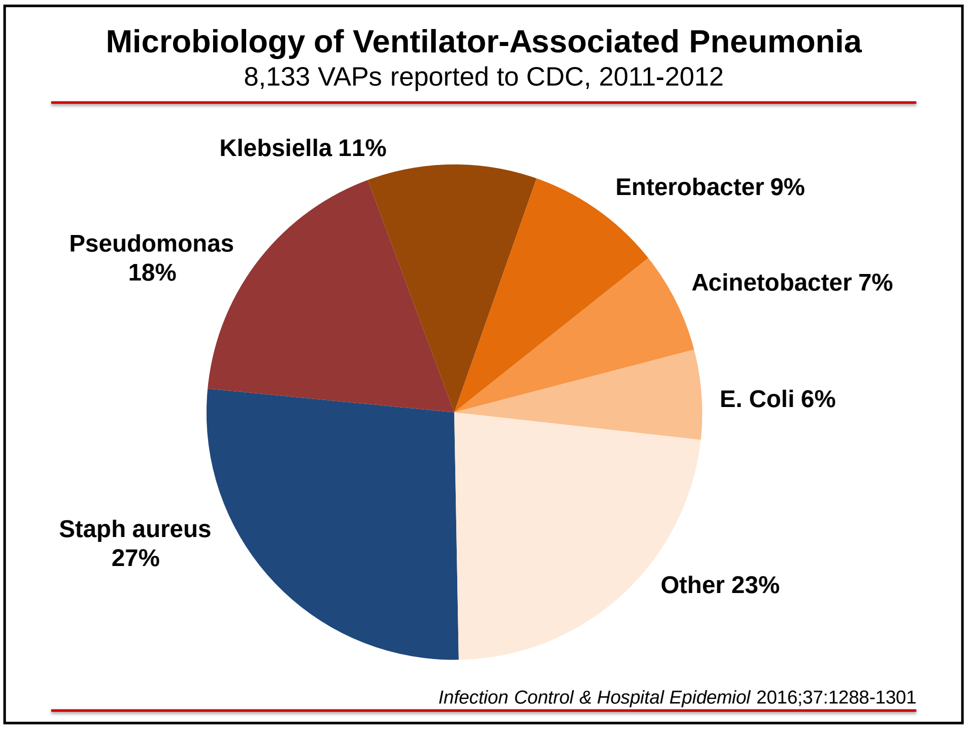
Is there any risk to de-escalation?

Retrospective analysis of 398 patients with suspected VAP



Chest 2006;129:1210-1218

What should we treat with?



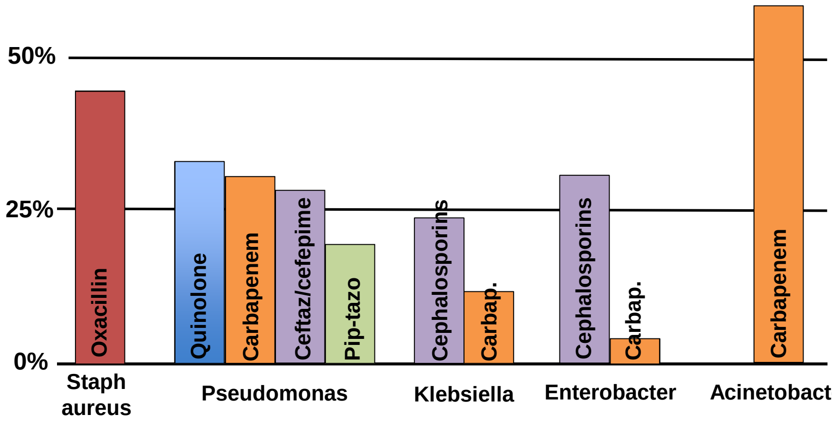
Microbiology of Ventilator-Associated Pneumonia

8,133 VAPs reported to CDC, 2011-2012

Infection Control & Hospital Epidemiol 2016;37:1288-1301

Resistance Rates for VAP Pathogens

8,133 VAPs reported to CDC, 2011-2012



Infection Control & Hospital Epidemiol 2016;37:1288-1301

HALF

FULL?

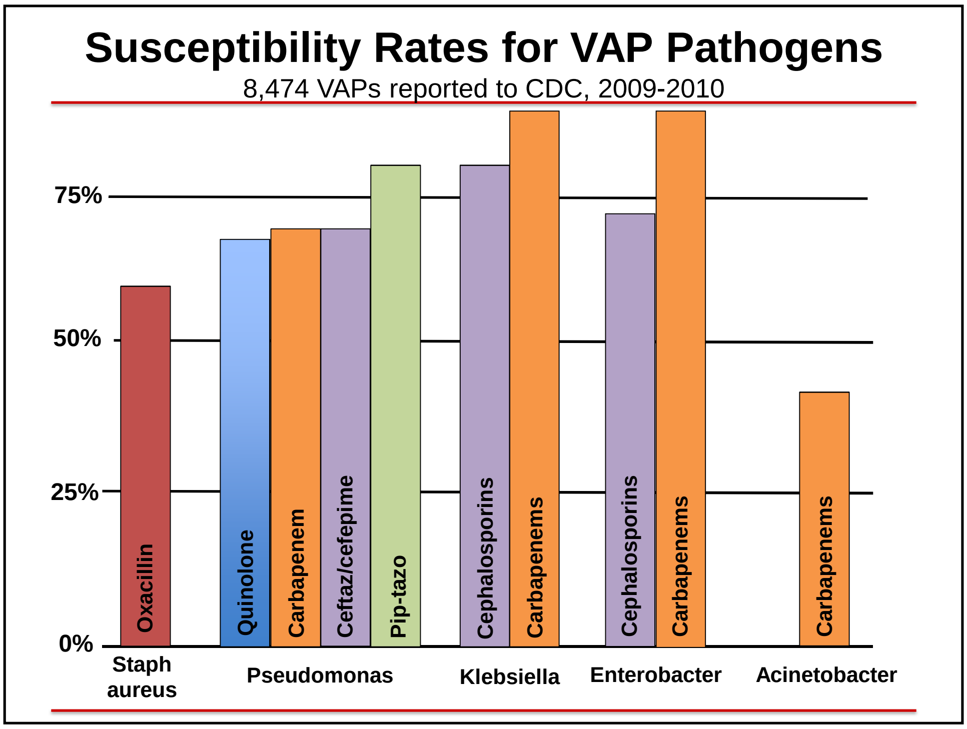
or

HALF

EMPTY

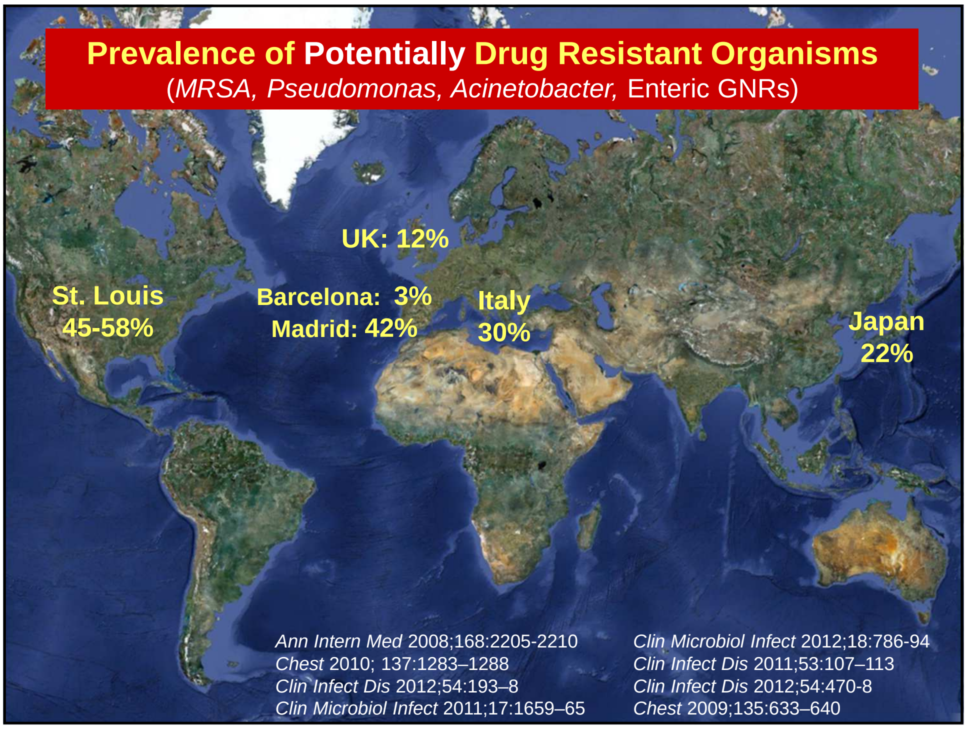
?

http://www.firstclassfashionista.com/wp-content/uploads/2011/10/Glass-of-Water.jpg



Susceptibility Rates for VAP Pathogens

8,474 VAPs reported to CDC, 2009-2010



Prevalence of Potentially Drug Resistant Organisms

(*MRSA, Pseudomonas, Acinetobacter,* Enteric GNRs)

UK: 12%
St. Louis 45-58%
Barcelona: 3%
Madrid: 42%
Italy 30%
Japan 22%

Ann Intern Med 2008;168:2205-2210
Chest 2010; 137:1283–1288
Clin Infect Dis 2012;54:193–8
Clin Microbiol Infect 2011;17:1659–65

Clin Microbiol Infect 2012;18:786-94
Clin Infect Dis 2011;53:107–113
Clin Infect Dis 2012;54:470-8
Chest 2009;135:633–640

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

2016

- **Know your local antibiogram and distribution of VAP pathogens**
- **Treat with agent(s) that will cover *Staph aureus* and *Pseudomonas***
- **Use a regimen that will be active against 90-95% of pneumonias**
  - Include MRSA coverage if local prevalence of MRSA >20%, risk factors for MDR pathogens, mechanical ventilation, or septic shock
  - Use two anti-Pseudomonal agents if >10% of Gram negatives resistant against to an agent being considered for monotherapy, risk factors for MDR pathogens, or septic shock

---

So what should we treat with?

Predicted Likelihood of Coverage

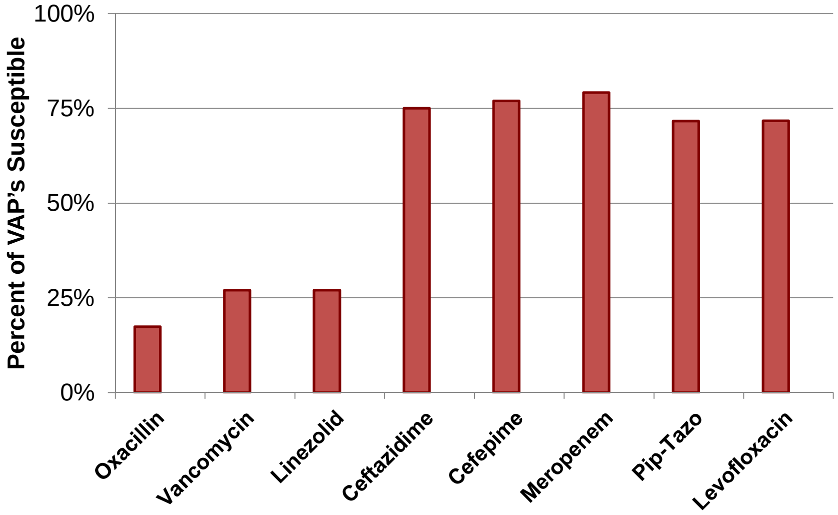
Susceptibility to Proposed Agent

X

Organism Frequency

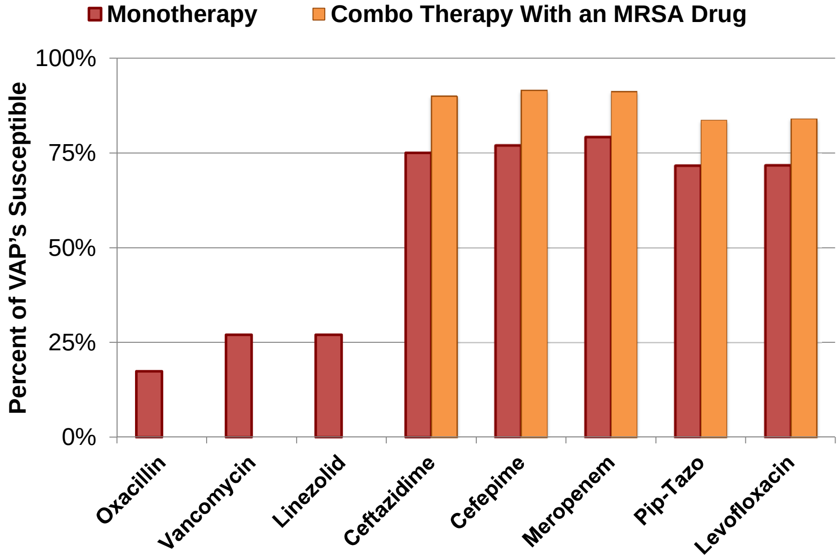
Predicted Likelihood of Active Coverage

Brigham and Women's Hospital, Boston, USA



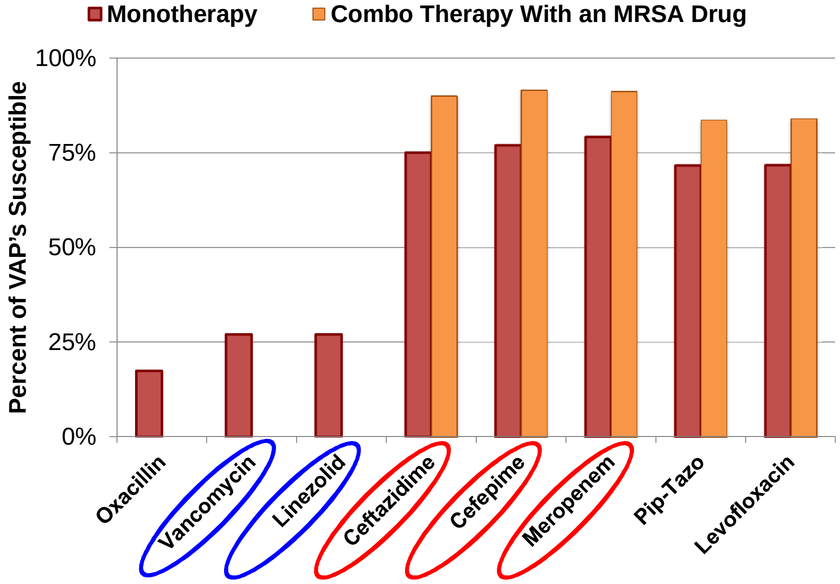
Predicted Likelihood of Active Coverage

Brigham and Women's Hospital, Boston, USA



Predicted Likelihood of Active Coverage

Brigham and Women's Hospital, Boston, USA



The Take Home for Empiric Treatment

- **Empiric treatment should include:**
  - Something for MRSA (vancomycin or linezolid)

  and

  - Something for Gram negatives including Pseudomonas (cefepime, ceftazidime, or meropenem in my hospital)

- **Add a second anti-Pseudomonal drug if:**
  - Higher local probability of Pseudomonas resistance
  - Known colonization with resistant pathogens
  - Septic shock
  - ARDS before pneumonia
  - Prolonged hospitalization
  - Acute renal replacement therapy prior to VAP

Should we get cultures?

Absolutely!

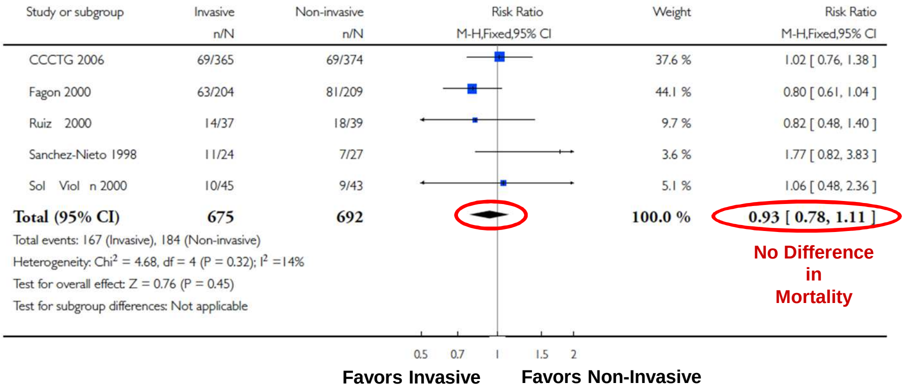
Positive cultures will allow you to tailor therapy.

Negative cultures may help facilitate stopping abx early.

Cultures essential to help us track pathogen frequency and resistance rates.

Invasive vs Non-Invasive Cultures

Impact on Mortality



Study or subgroup	Invasive n/N	Non-invasive n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CCCTG 2006	69/365	69/374		37.6 %	1.02 [0.76, 1.38]
Fagon 2000	63/204	81/209		44.1 %	0.80 [0.61, 1.04]
Ruiz 2000	14/37	18/39		9.7 %	0.82 [0.48, 1.40]
Sanchez-Nieto 1998	11/24	7/27		3.6 %	1.77 [0.82, 3.83]
Sol Viol n 2000	10/45	9/43		5.1 %	1.06 [0.48, 2.36]
Total (95% CI)	**675**	**692**		**100.0 %**	**0.93 [0.78, 1.11]**

Total events: 167 (Invasive), 184 (Non-invasive)

Heterogeneity: $\text{Chi}^2 = 4.68$, $df = 4$ ($P = 0.32$); $I^2 = 14\%$

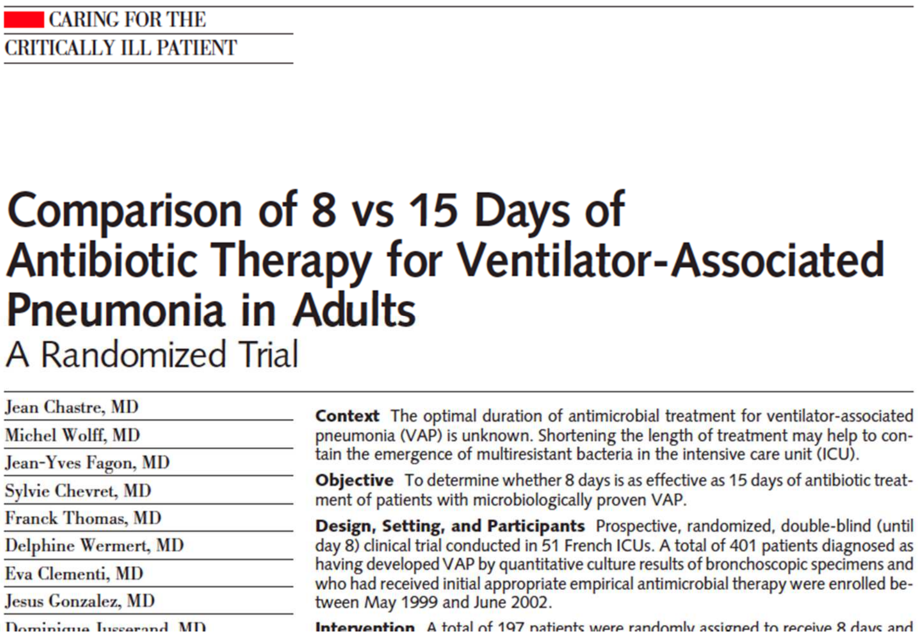
Test for overall effect: $Z = 0.76$ ($P = 0.45$)

Test for subgroup differences: Not applicable

No Difference in Mortality

Berton et al. Cochrane Database of Systematic Reviews 2014;10:CD006482

How long should we treat for?



CARING FOR THE
CRITICALLY ILL PATIENT

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

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Michel Wolff, MD
Jean-Yves Fagon, MD
Sylvie Chevret, MD
Franck Thomas, MD
Delphine Wermert, MD
Eva Clementi, MD
Jesus Gonzalez, MD
Dominique Jusserand, MD

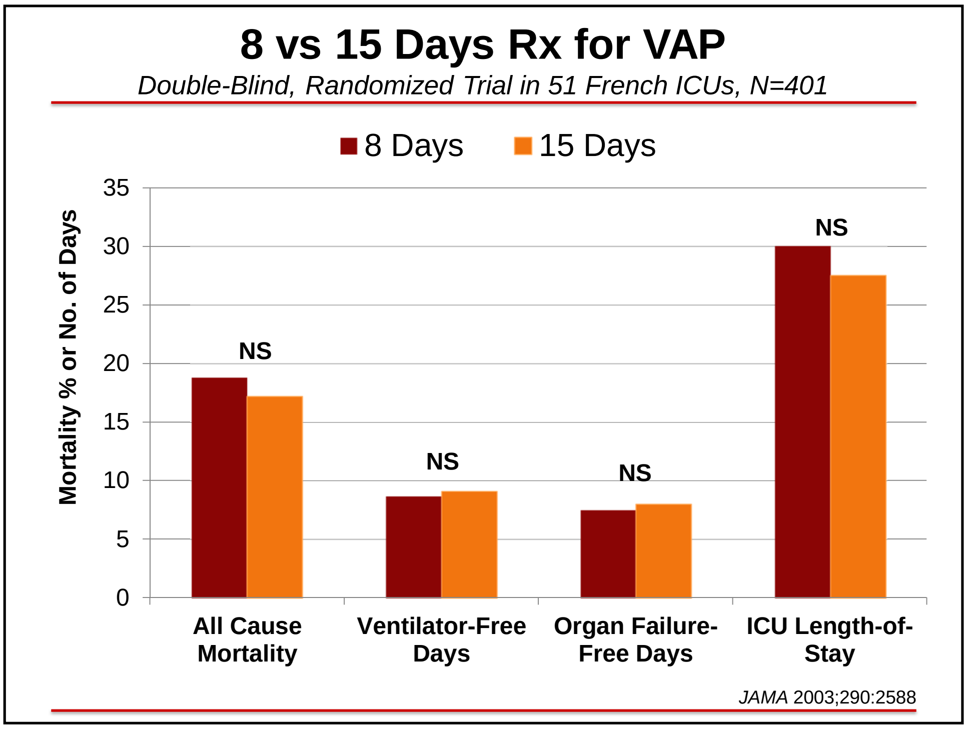
Context The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU).

Objective To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

Design, Setting, and Participants Prospective, randomized, double-blind (until day 8) clinical trial conducted in 51 French ICUs. A total of 401 patients diagnosed as having developed VAP by quantitative culture results of bronchoscopic specimens and who had received initial appropriate empirical antimicrobial therapy were enrolled between May 1999 and June 2002.

Intervention A total of 197 patients were randomly assigned to receive 8 days and

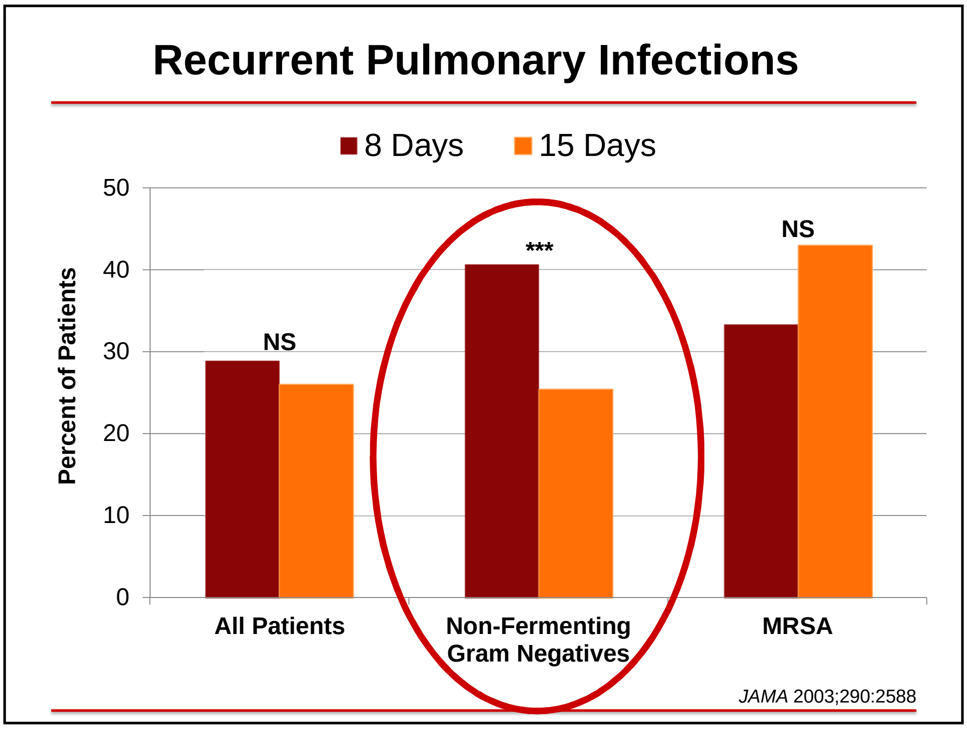
JAMA 2003;290:2588



8 vs 15 Days Rx for VAP

Double-Blind, Randomized Trial in 51 French ICUs, N=401

JAMA 2003;290:2588



Recurrent Pulmonary Infections

JAMA 2003;290:2588

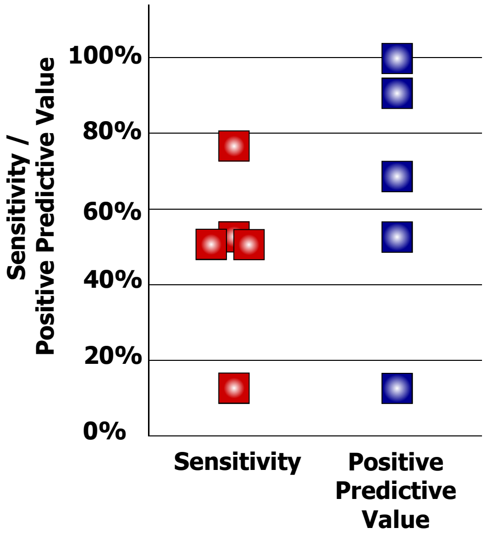
What Constituted a “Recurrent Pneumonia?”

- Defined using microbiological criteria:
- Repeat bronchoscopy with positive quantitative cultures
  - ≥10^4 CFU / ml for bronchoalveolar lavage
  - ≥10^3 CFU / ml for protected specimen brush

JAMA 2003;290:2588

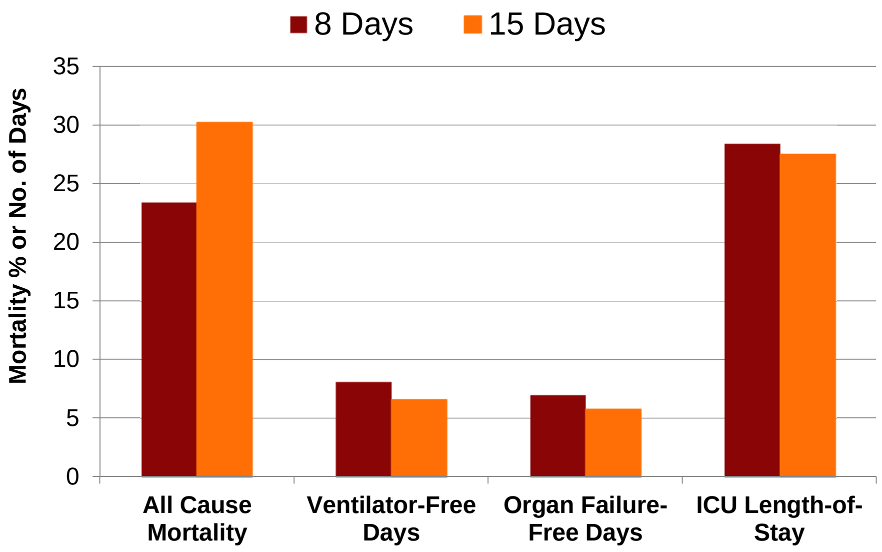
Accuracy of BAL cultures

Relative to histology



Kirtland, *Chest* 1997;112:445
Fabregas, *Thorax* 1999;54:867
Chastre, *Am Rev Respir Dis* 1984;130:924
Torres, *Am J Resp Crit Care Med* 1994;149:324
Marquette, *Am J Resp Crit Care Med* 1995;151:1878
Papazian, *Am J Resp Crit Care Med* 1995;152:1982

Clinical Outcomes in Patients with Non-Fermenting Gram Negative Bacilli



JAMA 2003;290:2588

Is less than 8 days feasible?

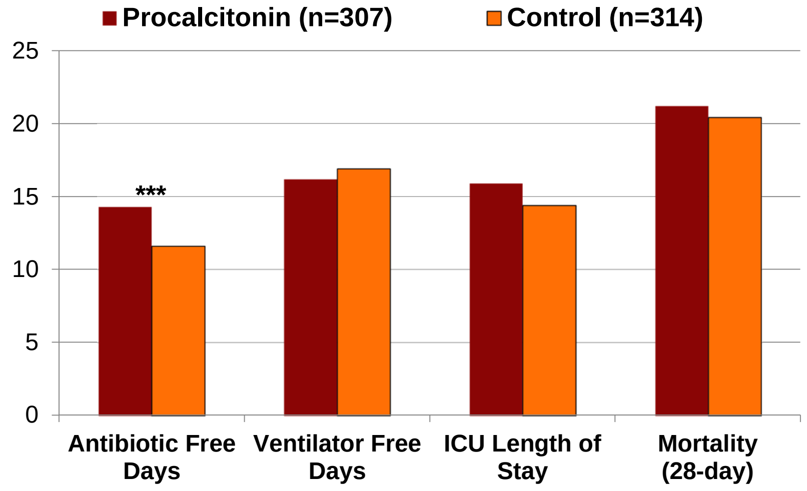
Experience with Early Discontinuations

- 81 patients randomized to standard therapy versus early discontinuation if clinical signs normalized at 3 days
  - No difference in ICU length of stay or mortality
- 290 patients randomized to standard therapy vs early discontinuation if alternative diagnosis OR resolution of clinical signs
  - Abx stopped early in 89% of intervention group
  - No difference ICU LOS, duration of ventilation, mortality

Am J Resp Crit Care Med 2000;162:505
Chest 2004;125:1791

Procalcitonin Surveillance: PRORATA

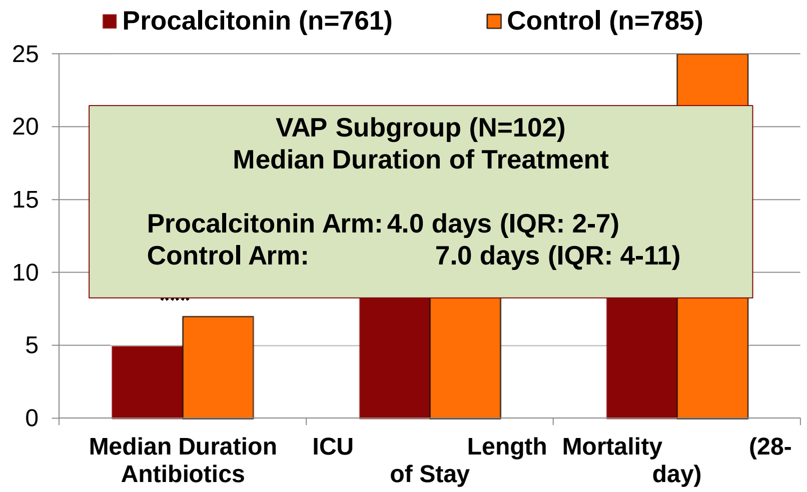
621 critically ill patients, open label RCT, 8 ICUs, France



Lancet 2010;375:463-474

Procalcitonin Surveillance: SAPS

1575 critically ill patients, open label RCT, 15 ICUs, Netherlands



VAP Subgroup (N=102)
Median Duration of Treatment

Procalcitonin Arm: 4.0 days (IQR: 2-7)
Control Arm: 7.0 days (IQR: 4-11)

Lancet Infect Dis 2016;16:819-827

VAP with Minimal and Stable Vent Settings

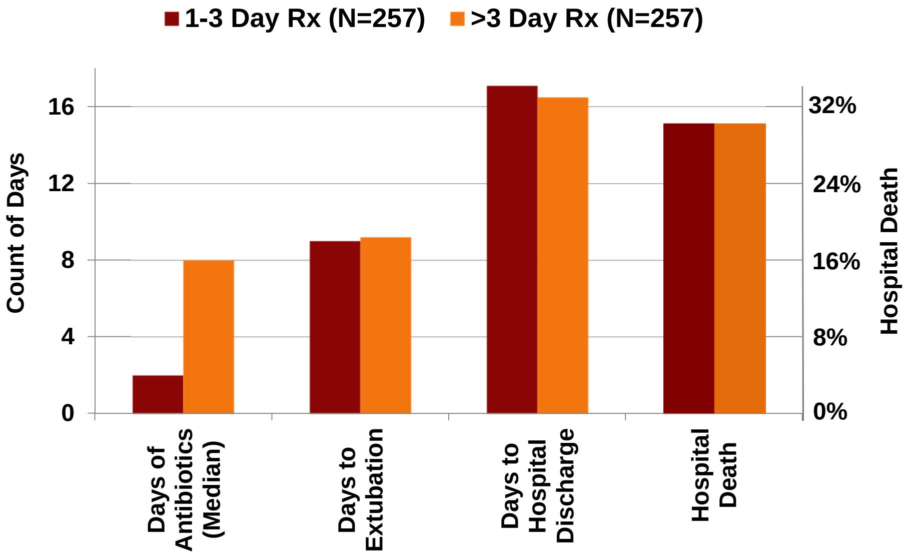
- Severe pneumonia typically impairs gas exchange.
- Severe VAPs therefore often require higher levels of ventilator support (⇧PEEP, ⇧FiO2, etc.)
- If a patient has stable and minimal ventilator settings (PEEP ≤5cm H_2O, FiO2 ≤40%) despite a new pneumonia perhaps that's an indication that the pneumonia is mild (or that the patient doesn't have pneumonia)
- Can one assess serial ventilator settings then to identify potential candidates for shorter courses of antibiotics?

Retrospective, Propensity-Matched Analysis
Brigham and Women's Hospital, 2006-2014

- **30,336 episodes of mechanical ventilation**
    - 2,549 met the study definition for VAP (8.4%)
    - 1,290 with minimal and stable vent settings (50% of VAPs)
- **514 propensity-matched patients with clinically-suspected VAP but minimal and stable ventilator settings**
    - 257 treated with 1-3 days of antibiotics
    - 257 treated with >3 days of antibiotics
- **Well-matched on age, sex, race-ethnicity, unit type, comorbidities, severity of illness, time to VAP, temperature, WBC count, use of vasopressors, neutrophils on Gram stain, and pathogens**

Clin Infect Disease 2017;64:870-876

VAP with Minimal and Stable Ventilator Settings



Clin Infect Disease *2017; ePub ahead of print*

How can we prevent ventilator-associated pneumonias?

The Classic Ventilator Bundle

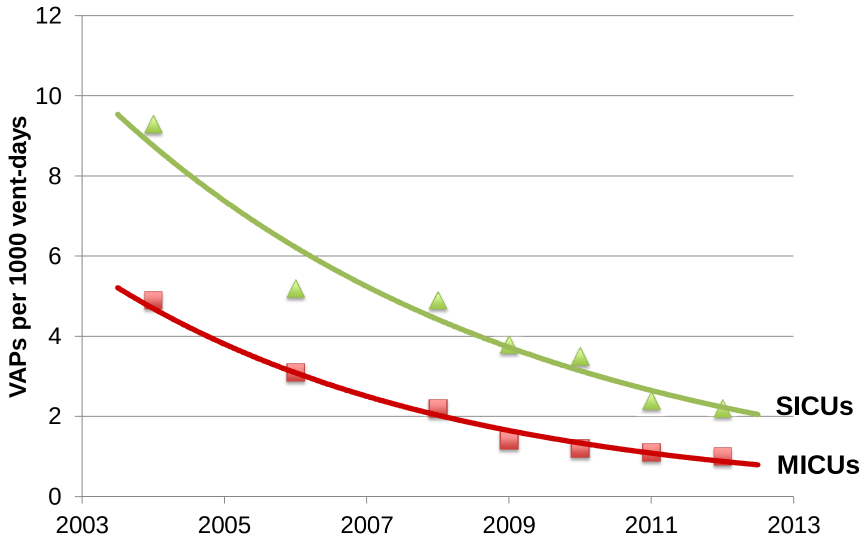
Elevate the head of the bed
Daily sedative interruptions
Daily assessment of readiness to wean
Stress ulcer prophylaxis
DVT prophylaxis
Oral care with chlorhexidine

100k *lives* Campaign
SOME IS NOT A NUMBER. SOON IS NOT A TIME.

PROTECTING
5 Million *lives*
FROM HARM
SOME IS NOT A NUMBER. SOON IS NOT A TIME.

U.S. National VAP Rates

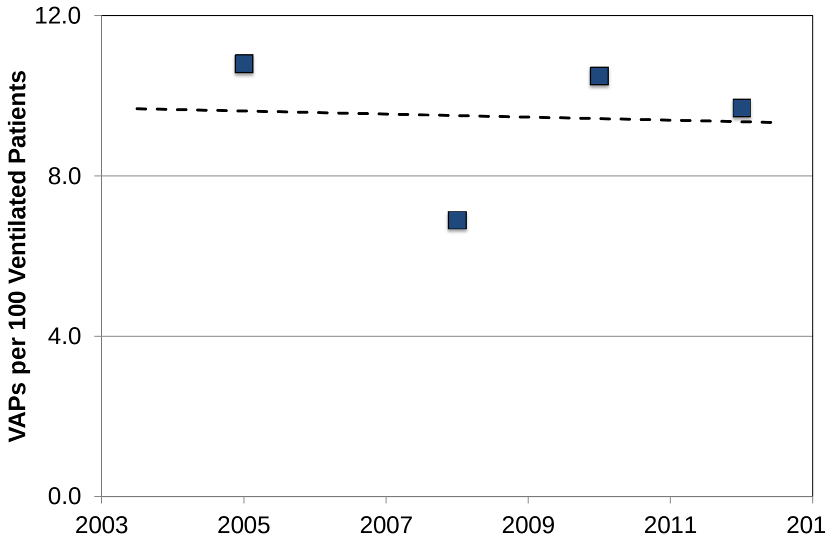
Cases Reported to CDC by Hospitals, 2004-2012



Source: CDC NNIS and NHSN

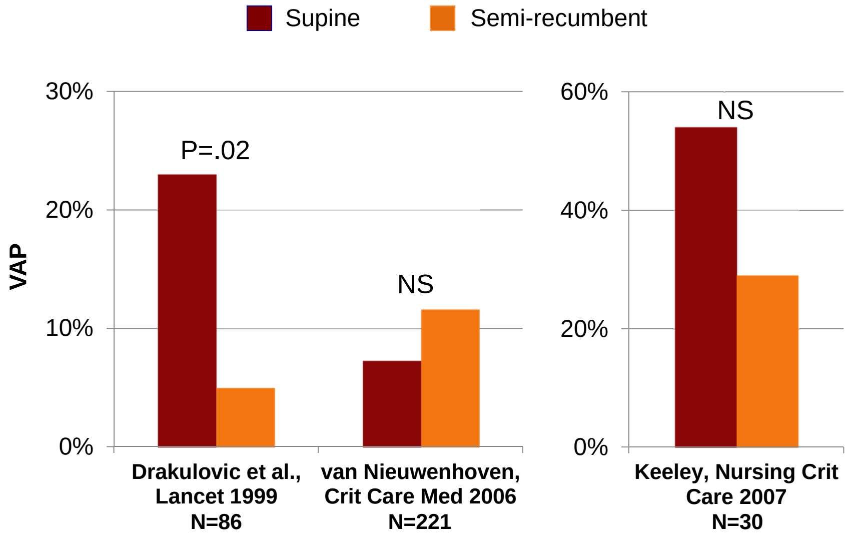
U.S. National VAP Rates

U.S Government Audits, 2005-2013



JAMA 2016;ePub ahead of print

Head-of-Bed Elevation and VAP Rates



Stress Ulcer Prophylaxis

Some studies suggest higher risk for pneumonia

- **Prospective cohort study of 63,878 admission to Beth Israel Deaconess Hospital in Boston**
  - Adjusted odds of hospital-acquired pneumonia 1.3 (95% CI 1.1-1.4) in acid-suppressant exposed vs unexposed patients

JAMA 2009;301:2120-2128

- **Case-control study of cardiothoracic surgery patients comparing patients on pantoprazole vs ranitidine (N=834)**
  - Adjusted odds of pneumonia 6.6 (95% CI 2.9-14.9) in patients on pantoprazole vs those on ranitidine

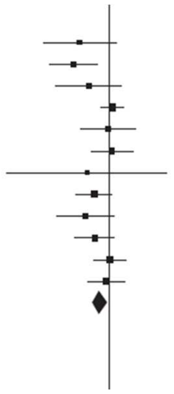
Chest 2009;136:440-447

- **Propensity matched analysis of 31,302 patients with severe sepsis**
  - Patients who received stress ulcer prophylaxis ~20% more likely to develop hospital acquired pneumonia

Critical Care Medicine 2016;44:e464-469

Oral Care with Chlorhexidine

Meta-analysis of RCTs: *lower* VAP rates



Chlorhexidine						
De Riso et al (1996)[18]	3	173	9	180	3·8%	0·35 (0·10–1·26)
Fourrier et al (2000)[13]	5	30	18	30	7·0%	0·28 (0·12–0·65)
Houston et al (2002)[20]	4	270	9	291	4·4%	0·48 (0·15–1·54)
MacNaughton et al (2004)[22]	32	91	28	88	14·1%	1·11 (0·73–1·67)
Grap et al (2004)[14]	4	7	3	5	5·9%	0·95 (0·36–2·49)
Fourrier et al (2005)[19]	13	114	12	114	8·3%	1·08 (0·52–2·27)
Bopp et al (2006)[17]	0	2	1	3	0·9%	0·44 (0·03–7·52)
Koeman et al (2006)[21]	13	127	23	130	9·9%	0·58 (0·31–1·09)
Tantipong et al (2008)[23]	5	102	12	105	5·5%	0·43 (0·16–1·17)
Scannapieco et al (2009)[26]	14	116	12	59	8·8%	0·59 (0·29–1·20)
Bellisimo-Rodriguez et al (2009)[24]	16	64	17	69	10·6%	1·01 (0·56–1·83)
Panchabhai et al (2009)[25]	14	88	15	83	9·4%	0·88 (0·45–1·71)
Subtotal (95% CI)		**1184**		**1157**	**88·5%**	**0·72 (0·55–0·94)**
Total events	123		159			

Heterogeneity: τ^2=0·06, χ^2=15·54, df=11 (p=0·16); I^2=29%

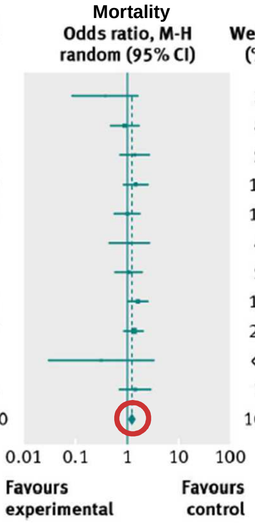
Test for overall effect: Z=2·40 (p=0·02)

Risk Ratio 0.72 (0.55-0.94)

Lancet Infectious Dis 2011;11:845

Oral Care with Chlorhexidine

Meta-Analysis of RCTs: *higher* mortality rates



Study	No of events/total Treatment	Control	Weight (%)	Mortality Odds ratio, M-H random (95% CI)
Fourier 2000	3/30	7/30	2	0.37 (0.08 to 1.58)
MacNaughton 2004	29/101	29/93	8	0.89 (0.48 to 1.64)
Fourrier 2005	31/114	24/114	9	1.40 (0.76 to 2.58)
Koeman 2006	49/127	39/130	12	1.47 (0.87 to 2.46)
Tantipong 2008	36/102	37/105	10	1.00 (0.57 to 1.77)
Scannapieco 2009	19/116	9/59	4	1.09 (0.46 to 2.58)
Bellissimo-Rodrigues 2009	35/98	33/96	9	1.06 (0.59 to 1.91)
Munro 2009	69/275	47/272	18	1.60 (1.06 to 2.43)
Panchabhai 2009	78/224	70/247	21	1.35 (0.91 to 2.00)
Cabov 2010	1/30	3/30	<1	0.31 (0.03 to 3.17)
Berry 2011	17/71	28/154	7	1.42 (0.72 to 2.80)
Total (95% CI)	367/1288	326/1330	100	1.25 (1.05 to 1.50)

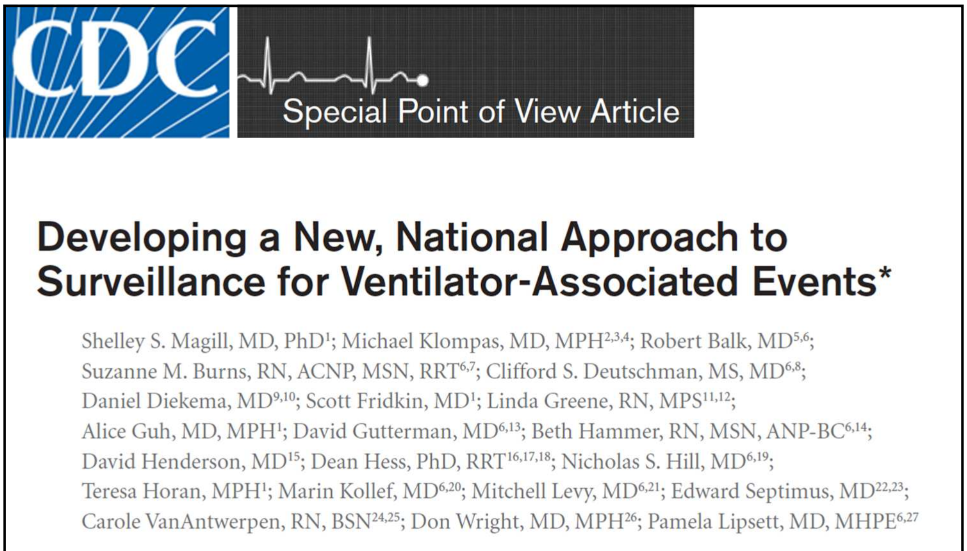
Test for heterogeneity: τ^2=0.00, χ^2=8.41, df=10, P=0.59, I^2=0%

Test for overall effect: z=2.47, P=0.01

Odds Ratio 1.25 (1.05-1.50)

BMJ 2014;348:g2197

Is VAP the best way to monitor and inspire better quality of care for ventilated patients?



Special Point of View Article

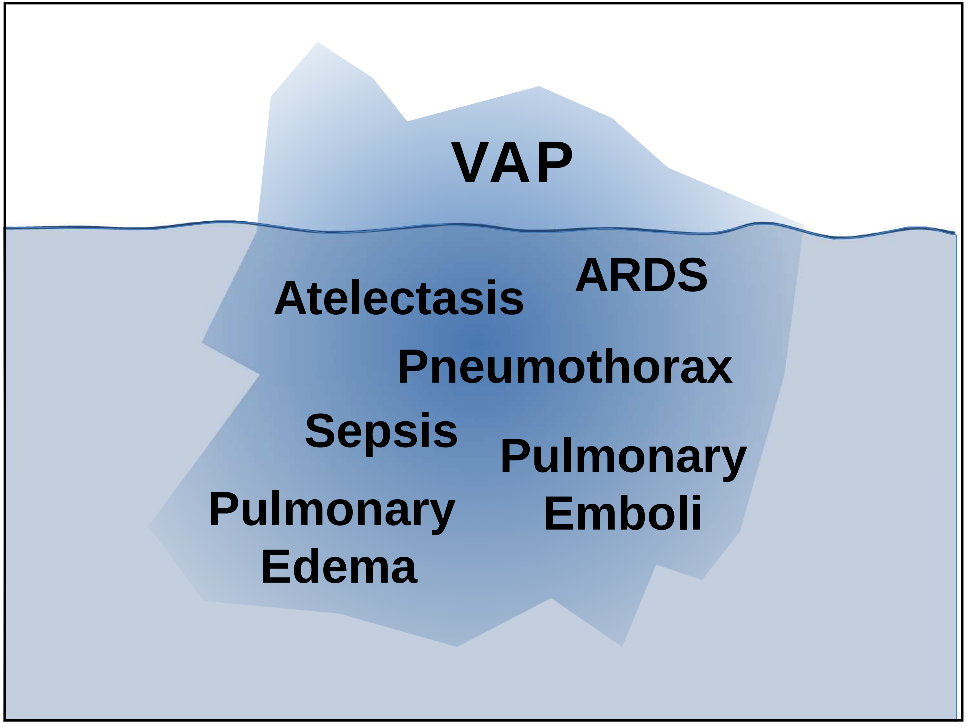
Developing a New, National Approach to Surveillance for Ventilator-Associated Events*

Shelley S. Magill, MD, PhD[1]; Michael Klompas, MD, MPH[2,3,4]; Robert Balk, MD[5,6];
Suzanne M. Burns, RN, ACNP, MSN, RRT[6,7]; Clifford S. Deutschman, MS, MD[6,8];
Daniel Diekema, MD[9,10]; Scott Fridkin, MD[1]; Linda Greene, RN, MPS[11,12];
Alice Guh, MD, MPH[1]; David Gutterman, MD[6,13]; Beth Hammer, RN, MSN, ANP-BC[6,14];
David Henderson, MD[15]; Dean Hess, PhD, RRT[16,17,18]; Nicholas S. Hill, MD[6,19];
Teresa Horan, MPH[1]; Marin Kollef, MD[6,20]; Mitchell Levy, MD[6,21]; Edward Septimus, MD[22,23];
Carole VanAntwerpen, RN, BSN[24,25]; Don Wright, MD, MPH[26]; Pamela Lipsett, MD, MHPE[6,27]

Critical Care Medicine 2013;41:2467-2475

An Alternative Approach to Surveillance

- **Shift the focus of surveillance from pneumonia to the syndrome of ventilator complications**
  - More accurate description of what can be reliably determined using surveillance definitions
  - Emphasizes the importance of preventing ***all*** complications of mechanical ventilation, not just pneumonia
  - Improve objectivity
  - Enable the possibility of automated surveillance



VAP

Atelectasis

ARDS

Pneumothorax

Sepsis

Pulmonary Emboli

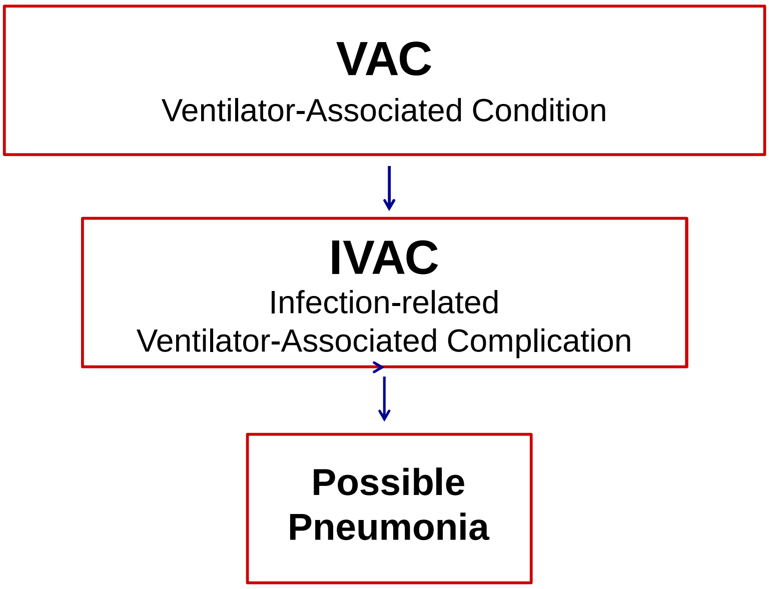
Pulmonary Edema

Ventilator-Associated Events (VAE)

Sustained rise in daily minimum PEEP ≥3cm or FiO2 ≥20 points after a period of stable or improving daily minimum PEEP or FiO2

Date	PEEP (min)	FiO2 (min)
Jan 1	10	100
Jan 2	5	50
Jan 3	5	40
Jan 4	5	40
Jan 5	8	60
Jan 6	8	50
Jan 7	8	40
Jan 8	5	40
Jan 9	5	40

VAE



VAC

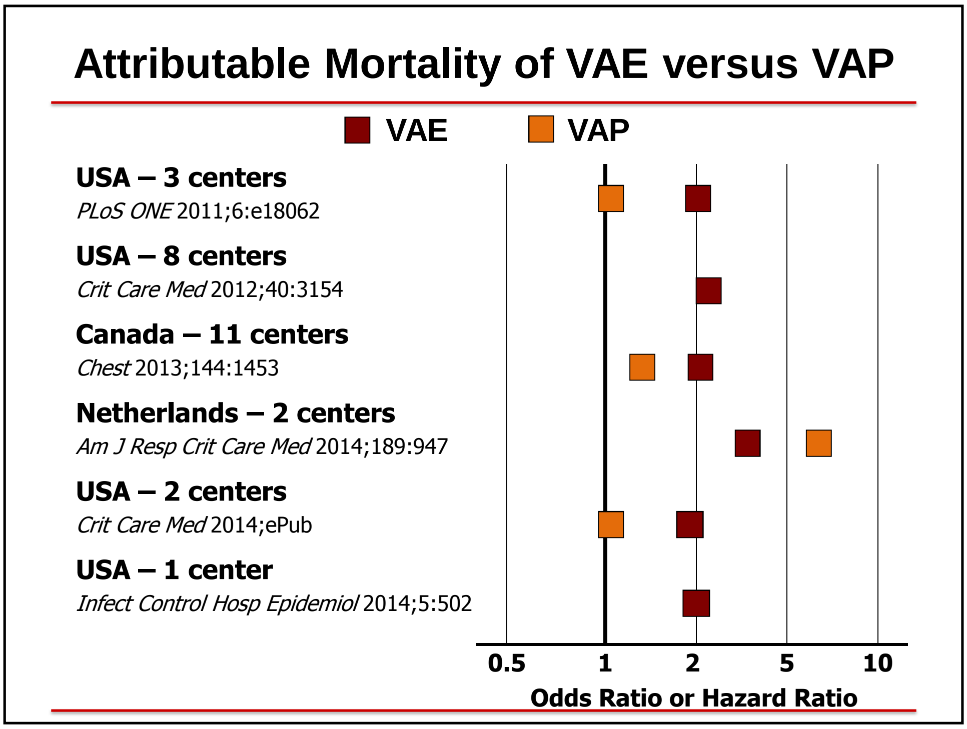
Ventilator-Associated Condition

IVAC

Infection-related

Ventilator-Associated Complication

Possible Pneumonia



Attributable Mortality of VAE versus VAP

🟥 VAE 🟧 VAP

USA – 3 centers
PLoS ONE 2011;6:e18062

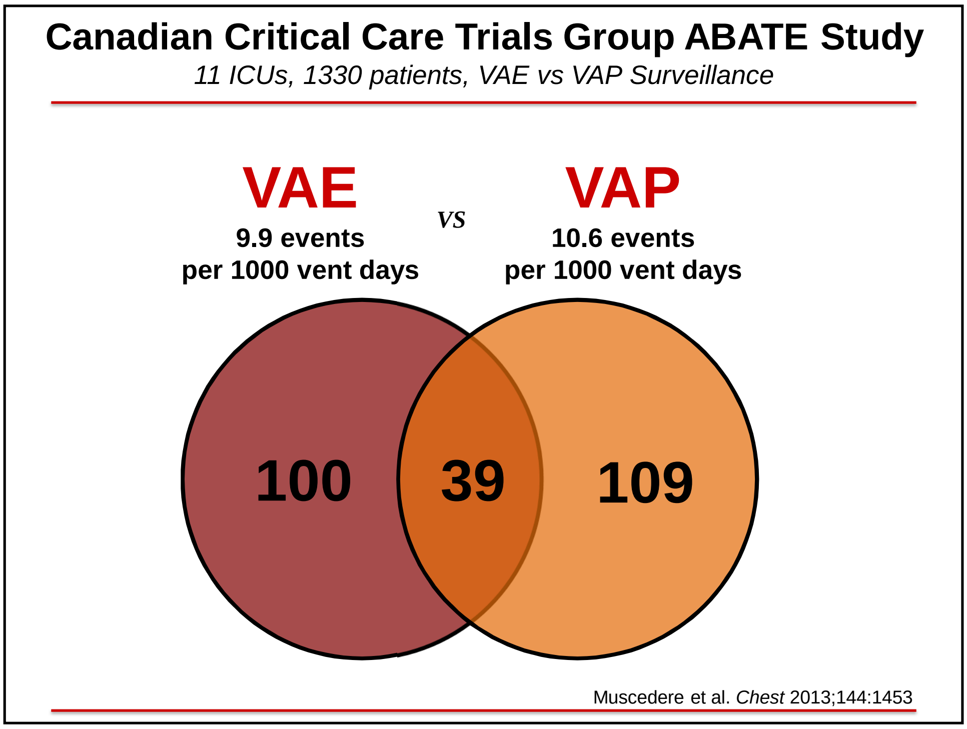
USA – 8 centers
Crit Care Med 2012;40:3154

Canada – 11 centers
Chest 2013;144:1453

Netherlands – 2 centers
Am J Resp Crit Care Med 2014;189:947

USA – 2 centers
Crit Care Med 2014;ePub

USA – 1 center
Infect Control Hosp Epidemiol 2014;5:502



Canadian Critical Care Trials Group ABATE Study

11 ICUs, 1330 patients, VAE vs VAP Surveillance

VAE
9.9 events
per 1000 vent days

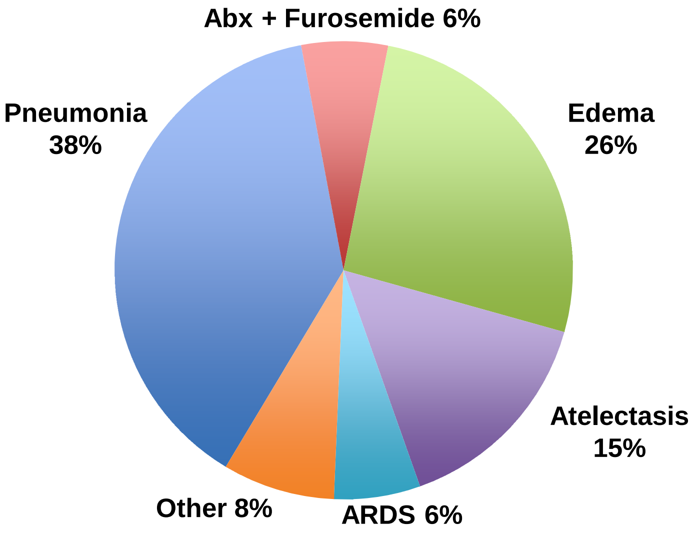
vs

VAP
10.6 events
per 1000 vent days

Muscedere et al. *Chest* 2013;144:1453

Qualitative analysis of 153 VAEs

Royal Brisbane & Women's Hospital, Queensland, Australia



Hayashi et al. *Clin Infect Dis* 2013;56:471-477

VAE = VAP +
Fluid +
ARDS +
Atelectasis

Fewer VAEs

http://www.macrobert.org/assets/images/Film/May%202013/WizardOfOz_214Pyxurz.jpg

How do we get there?

Strategies for Preventing VAEs

Decrease duration of mechanical ventilation

Target the primary conditions associated with VAEs

Strategies for Preventing VAEs

Minimize sedation

Paired SATs and SBTs

Early mobility

Low tidal volume ventilation

Conservative fluid management

Minimize blood transfusions

Summary

- Diagnosing pneumonia is very challenging. **We're often wrong.** CT may help.
- **Know your local antibiogram and distribution of VAP pathogens.**
- **Aim for an empiric regimen that will be active for at least 90-95% of patients**. Will likely need to include one agent active against MRSA (linezolid or vancomycin) and 1-2 agents active against Pseudomonas but **less may be suitable depending on your local distribution of pathogens and resistance.** Get cultures!
- **7-8 days of treatment usually adequate for all pathogens**. Shorter courses may be adequate for some patients – procalcitonin and / or analysis of vent settings may help identify candidates for shorter courses.
- CDC created **ventilator-associated events (VAEs)** to enhance objectivity, facilitate automation, and expand prevention efforts for ventilated patients
  - VAEs usually caused by pneumonia, ARDS, atelectasis or pulmonary edema
- Best practices to prevent VAEs include minimizing sedation, SATs, SBTs, early mobility, low tidal volume ventilation, and conservative fluid management

Review questions

- A 76 year old diabetic woman with a history of congestive heart failure is admitted to a surgical ICU on a ventilator following a motor vehicle accident. She was the unrestrained driver of the car. She suffered multiple fractures of her ribs and right femur. She is emergently taken to the OR for open reduction and internal fixation of her femur fracture. Two days later she develops fever, tachypnea, increased oxygen requirement. The nurse reports increased secretions from the endotracheal tube. Lung sounds are obscured by the ventilator. She has moderate anasarca. Her WBC count is 17. A portable chest x-ray shows bilateral lower lobe opacities. You take cultures of blood, urine, and endotracheal tube aspirates. You administer furosemide and begin empiric treatment for possible ventilator-associated pneumonia with vancomycin and cefepime.

Question 1 Continued

One day later, the patient is improving. Her fever persists but her WBC count has normalized and she is requiring minimal support from the ventilator. Her chest x-ray still shows some opacities in the lower lobes but they are less pronounced. All cultures are negative. At this point would you:

a) Continue vancomycin and cefepime for 8 days total
b) Switch vancomycin to linezolid, continue cefepime
c) De-escalate to cefepime alone
d) Switch to ciprofloxacin alone
e) Stop all antibiotics

Question 1 Answer

a) Continue vancomycin and cefepime for 8 days total
b) Switch vancomycin to linezolid, continue cefepime
c) De-escalate to cefepime alone
d) Switch to ciprofloxacin alone
e) Stop all antibiotics

The patient's rapid improvement argues against a true pneumonia. The majority of patients with the constellation of signs for VAP do not have pneumonia on histology. In this patient's case, her fever could be post-op and her infiltrates due to pulmonary contusion, pulmonary edema, and/or atelectasis. Stop all antibiotics to minimize risk of selecting for resistant pathogens.

Question 2

A 67 year old man with a history of cholangiocarcinoma is admitted to hospital with fever, confusion, and hypotension. Labs are notable for leukocytosis, thrombocytopenia, and an elevated bilirubin. Imaging is notable for biliary dilatation. He is emergently intubated and treated with antibiotics, fluids, and vasopressors. He undergoes emergent ERCP with placement of a biliary stent. He improves over the next two days but then develops recurrent fevers, increased secretions from the endotracheal tube, and worsening oxygenation. Chest X-ray suggests a new left lower lobe infiltrate. An endotracheal aspirate is positive for *Pseudomonas aeruginosa*. How long will you treat for?

a) 3 days
b) 5 days
c) 7 days
d) 14 days
e) 21 days

Question 2

A 67 year old man with a history of cholangiocarcinoma is admitted to hospital with fever, confusion, and hypotension. Labs are notable for leukocytosis, thrombocytopenia, and an elevated bilirubin. Imaging is notable for biliary dilatation. He is emergently intubate and treated with antibiotics, fluids, and pressors. He undergoes emergent ERCP with placement of a biliary stent. He improves over the next two days but then develops recurrent fevers, increased secretions from the endotracheal tube, and worsening oxygenation. Chest X-ray suggests a new left lower lobe infiltrate. An endotracheal aspirate is positive for *Pseudomonas aeruginosa*. How long will you treat for?

a) 3 days
b) 5 days
c) 7 days
d) 14 days
e) 21 days

Clinical outcomes in patients treated with 7-8 days of antibiotics are similar to those treated with 14-15 days for VAP due to Pseudomonas. Shorter course therapy is therefore preferred. Ultimate duration of treatment, however, should be tailored to each patient's clinical response. This could include shortening or extending treatment from the 7 day default.

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- Chastre J, Wolff M, Fagon JY, *et al*: **Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial**. *JAMA* 2003, **290**(19):2588-2598.
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Disclosures

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Infection, FUO, and Antibiotic use in the ICU

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No conflicts of interest

Background

- Fever is common in the ICU - ~ 30-70% of ICU patients have at least one fever during ICU stay
- Fever work-up is challenging – broad differential, difficult to distinguish infectious vs. non-infectious causes
- Fever in the ICU is expensive!
- Determining when to give empiric antibiotics can be difficult

Niven DJ et al. J Int Care Med 2012.

Definitions

- Fever = core body temp ≥ 38.3° C (101° F)
- High fever = core body temp ≥ 39.5° C (103.1° F)
- Prolonged fever = fever ≥ 5 days
- Gold standard for core temp measurement = by PA catheter
- Other accurate ways to measure temp in ICU = bladder catheters, esophageal probe, rectal thermometer
- Temperature measurement by TM or temporal artery thermometers are less accurate

Niven DJ et al. J Int Care Med 2012.

Epidemiology of fever in ICU

Compiled from 4 studies:

- 34-53% of fevers due to infection in ICUs (some medical, some surgical, some combined)
- Fever alone was associated with increased mortality (increased from 10% to 35%)
- Prolonged fever associated with increased mortality when compared with fever < 5 days (63% for prolonged fever vs. 30%)

Niven DJ et al. J Int Care Med 2012.

Elevated body temperature causes

- Hyperthermia syndromes
  - Drug-induced
  - Endocrine (thyrotoxicosis, pheochromocytoma, adrenal crisis)
  - Environmental (heatstroke)
- Infectious fever
  - Bacterial, fungal, viral, protozoa/parasitic
- Non-infectious fever
  - Many causes…

Work-up of fever in the ICU

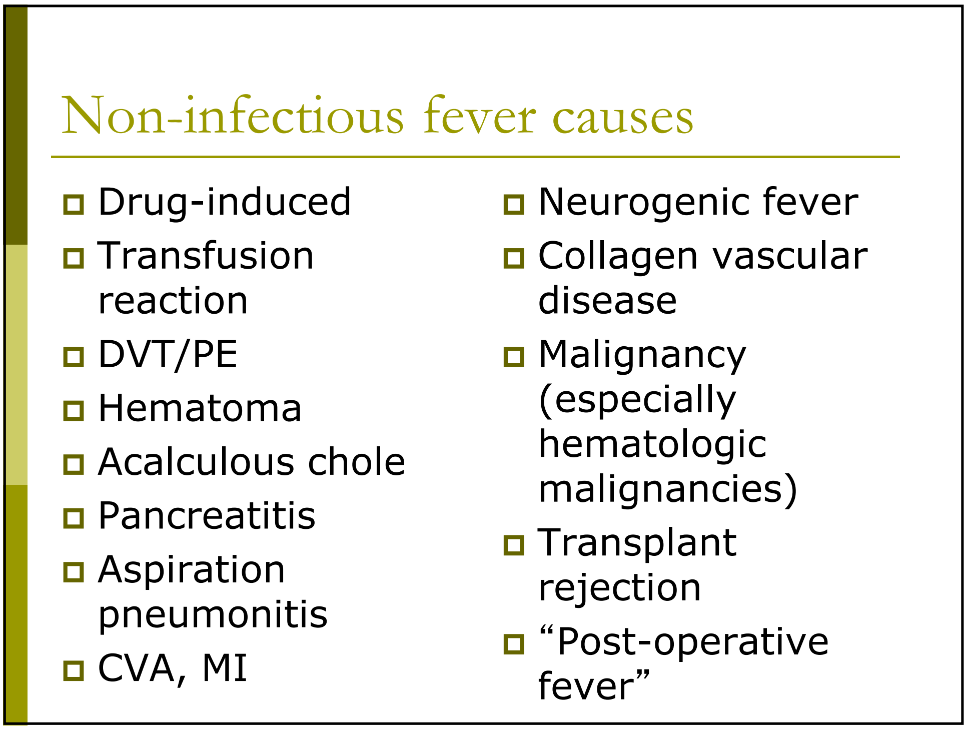
- Society of Critical Care Medicine together with the Infectious Disease Society of America:
  - "because fever can have many infectious and non-infectious etiologies, a new fever in a patient in the intensive care unit should trigger a careful clinical assessment rather than automatic orders for laboratory and radiographic tests."
- Review fever curve, timing of procedures, symptoms, physical exam, recent labs

Claridge JA, et al. Amer Surg 2009.

Drug-induced hyperthermia

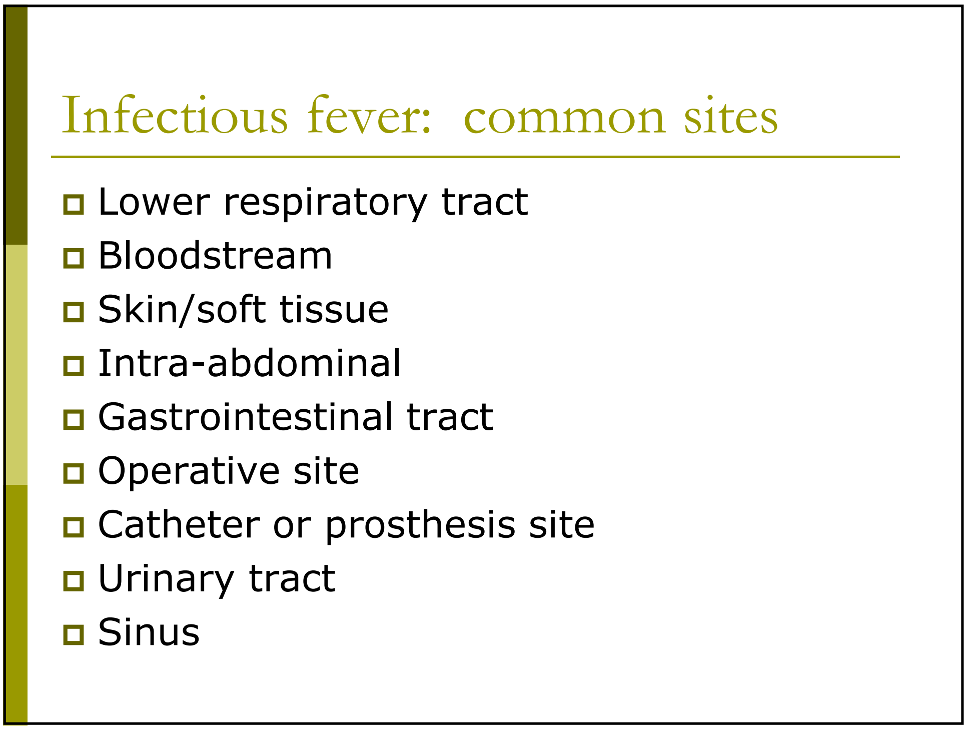
- Malignant hyperthermia: Rapid onset of muscle rigidity, hyperthermia and acidosis usually triggered by inhalational anesthetics and depolarizing paralytic agents
- Neuroleptic malignant syndrome: insidious onset of hyperthermia, muscle rigidity and mental status changes usually related to administration of neuroleptic agents
- Serotonin syndrome: hyperthermia and other signs of autonomic instability, cognitive and neuromuscular changes usually in patients taking selective serotonin reuptake inhibitors
- Adrenergic fever: due to amphetamines, MDMA, cocaine, MAOIs, theophyillne. Agitation + hyperthermia, treat with benzos.
- Baclofen withdrawl: 1-3 days after discontinuation of baclofen, muscle spasms + hyperthermia,

McAllen KJ, et al. Crit Care Med 2010.



Non-infectious fever causes

- Drug-induced
- Transfusion reaction
- DVT/PE
- Hematoma
- Acalculous chole
- Pancreatitis
- Aspiration pneumonitis
- CVA, MI
- Neurogenic fever
- Collagen vascular disease
- Malignancy (especially hematologic malignancies)
- Transplant rejection
- “Post-operative fever”



Infectious fever: common sites

- Lower respiratory tract
- Bloodstream
- Skin/soft tissue
- Intra-abdominal
- Gastrointestinal tract
- Operative site
- Catheter or prosthesis site
- Urinary tract
- Sinus

Common infection sites

- **Lower respiratory tract**
- **Bloodstream**
- Skin/soft tissue
- Intra-abdominal
- Gastrointestinal tract
- Operative site
- Catheter or prosthesis site
- Urinary tract
- Sinus

ATA/IDSA update

- Paradigm for pneumonia changed in 2016:

- No more HCAP
- CAP or HAP or VAP

- CAP – treat for 5 days (or less)
- HAP or VAP – treat for 7 days (or less)

https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw353

Lower respiratory tract infections

- HAP = hospital-acquired pneumonia
- VAP = ventilator-associated pneumonia
- HAP = 25% of all ICU infections (and > 50% of antibiotics given in ICUs)
- 10-25% of intubated patients develop VAP
- Risk of VAP is highest earlier in the course of hospitalization
- Attributable mortality to HAP ~ 33-50%

https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw353

Pneumonia - bugs

- Strep pneumo
- Staph aureus
  - MRSA? Concern if known colonized or prior infection, necrotizing pneumonia, new vent requirement, septic shock
- Enteric gram-negative rods
- Non-enteric GNR (eg Pseudomonas)
  - Concern for MDR organisms if: structural lung disease, prior colonization/infection, immune deficiency,
- Viral!!! (influenza, RSV, and more..)

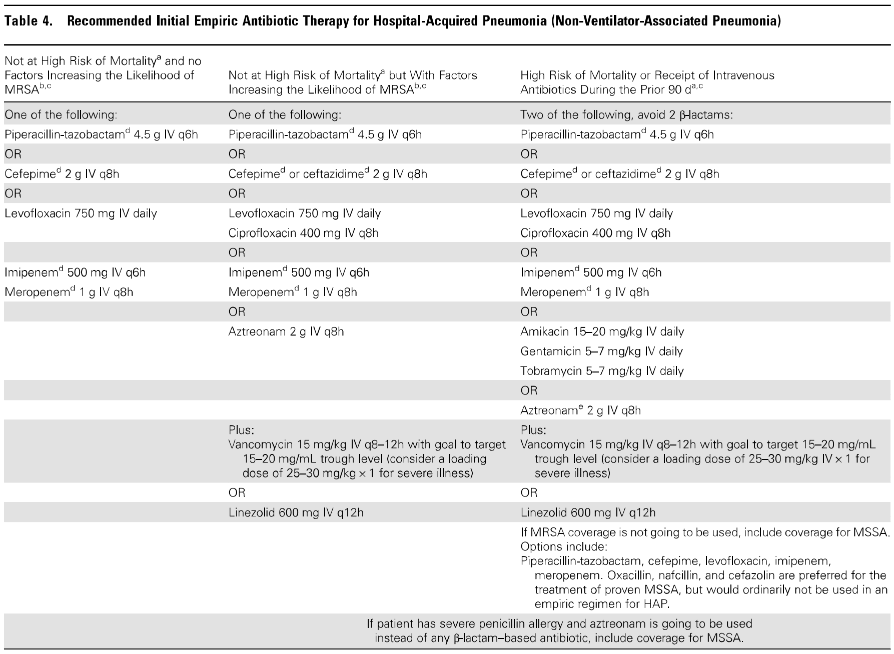


Table 4. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[a,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h
OR	OR	OR
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h
Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15–20 mg/kg IV daily
		Gentamicin 5–7 mg/kg IV daily
		Tobramycin 5–7 mg/kg IV daily
		OR
		Aztreonam[e] 2 g IV q8h
	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA. Options include: Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam–based antibiotic, include coverage for MSSA.		

https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw353

VAP – empiric antibiotics

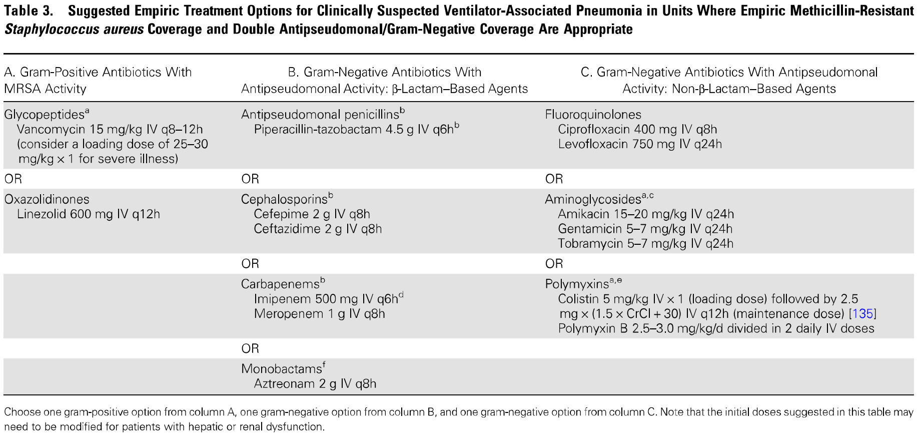


Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.

https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw353

HAP/VAP: evaluation

- Clinical evaluation (fever, respiratory status/vent settings, physical exam), leukocytosis, CXR, and lower respiratory tract culture
- Some organisms almost never cause pneumonia:

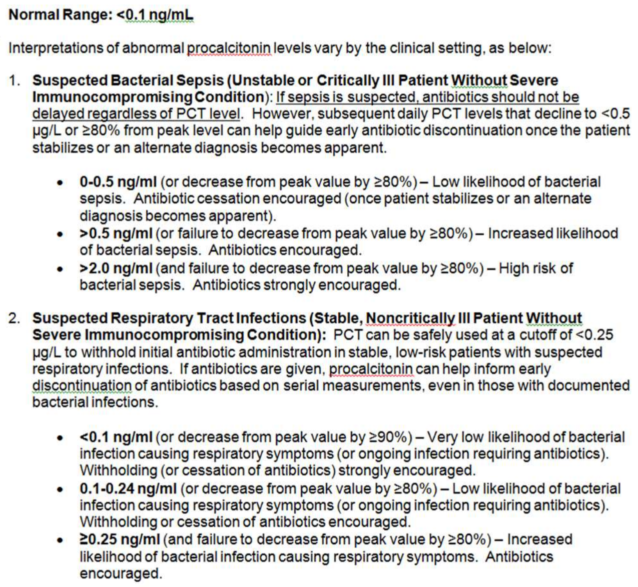
  Enterococci, viridans streptococci, coagulase-negative staphlococci and *Candida* species.
- Make sure the sputum represents a deep specimen (many WBC/PMN, few Epis)
- ICU studies: respiratory tract sample culture for diagnosis of HAP/VAP have widely variable sensitivity and specificity
- Procalcitonin?

Procalcitonin

- Biomarker of infection
  - Precursor to hormone calcitonin
  - Rises in response to proinflammatory state, particularly bacterial infections
  - More specific to bacterial infection than other biomarkers (eg CRP)
- Correlated with bacterial infection in studies of patients with respiratory tract infections and sepsis
- Followed daily to guide antibiotic course length and facilitate de-escalation

Rhee C, Open Forum Infectious Disease 2016.

Procalcitonin - interpretation

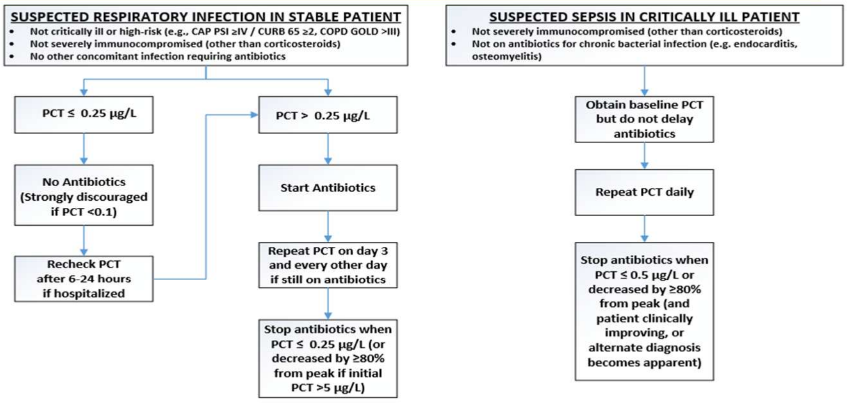


Normal Range: <0.1 ng/mL

Interpretations of abnormal procalcitonin levels vary by the clinical setting, as below:

1. **Suspected Bacterial Sepsis (Unstable or Critically Ill Patient Without Severe Immunocompromising Condition)**: If sepsis is suspected, antibiotics should not be delayed regardless of PCT level. However, subsequent daily PCT levels that decline to <0.5 µg/L or ≥80% from peak level can help guide early antibiotic discontinuation once the patient stabilizes or an alternate diagnosis becomes apparent.
    - **0-0.5 ng/ml** (or decrease from peak value by ≥80%) – Low likelihood of bacterial sepsis. Antibiotic cessation encouraged (once patient stabilizes or an alternate diagnosis becomes apparent).
    - **>0.5 ng/ml** (or failure to decrease from peak value by ≥80%) – Increased likelihood of bacterial sepsis. Antibiotics encouraged.
    - **>2.0 ng/ml** (and failure to decrease from peak value by ≥80%) – High risk of bacterial sepsis. Antibiotics strongly encouraged.
2. **Suspected Respiratory Tract Infections (Stable, Noncritically Ill Patient Without Severe Immunocompromising Condition):** PCT can be safely used at a cutoff of <0.25 µg/L to withhold initial antibiotic administration in stable, low-risk patients with suspected respiratory infections. If antibiotics are given, procalcitonin can help inform early discontinuation of antibiotics based on serial measurements, even in those with documented bacterial infections.
    - **<0.1 ng/ml** (or decrease from peak value by ≥90%) – Very low likelihood of bacterial infection causing respiratory symptoms (or ongoing infection requiring antibiotics). Withholding (or cessation of antibiotics) strongly encouraged.
    - **0.1-0.24 ng/ml** (or decrease from peak value by ≥80%) – Low likelihood of bacterial infection causing respiratory symptoms (or ongoing infection requiring antibiotics). Withholding or cessation of antibiotics encouraged.
    - **≥0.25 ng/ml** (and failure to decrease from peak value by ≥80%) – Increased likelihood of bacterial infection causing respiratory symptoms. Antibiotics encouraged.

Procalcitonin – one suggested algorithm for interpretation



SUSPECTED RESPIRATORY INFECTION IN STABLE PATIENT
- Not critically ill or high-risk (e.g., CAP PSI ≥IV / CURB 65 ≥2, COPD GOLD >III)
- Not severely immunocompromised (other than corticosteroids)
- No other concomitant infection requiring antibiotics

PCT ≤ 0.25 µg/L

No Antibiotics (Strongly discouraged if PCT <0.1)

Recheck PCT after 6-24 hours if hospitalized

PCT > 0.25 µg/L

Start Antibiotics

Repeat PCT on day 3 and every other day if still on antibiotics

Stop antibiotics when PCT ≤ 0.25 µg/L (or decreased by ≥80% from peak if initial PCT >5 µg/L)

SUSPECTED SEPSIS IN CRITICALLY ILL PATIENT
- Not severely immunocompromised (other than corticosteroids)
- Not on antibiotics for chronic bacterial infection (e.g. endocarditis, osteomyelitis)

Obtain baseline PCT but do not delay antibiotics

Repeat PCT daily

Stop antibiotics when PCT ≤ 0.5 µg/L or decreased by ≥80% from peak (and patient clinically improving, or alternate diagnosis becomes apparent)

Notes:
- *If PCT levels do not decline despite therapy, consider treatment failure (e.g., inadequate antibiotic therapy or source control).*
- *PCT algorithms apply to patients with clinically confirmed infections as well as those in whom infection was never proven.*
- *False positives can occur from noninfectious conditions that cause systemic inflammation, such as severe trauma, circulatory shock, major surgery, burns, inhalation injury, and pancreatitis.*
- *False negatives can occur early in the course of disease, or in contained localized infections (e.g. mediastinitis, empyema, abscesses).*
- *In addition to immunocompromising conditions, pregnancy and cystic fibrosis are two conditions that have typically been used as exclusion criteria in most PCT trials.*
- ***PCT algorithms can be used as a clinical decision aid but should never override clinical judgment.***

Procalcitonin - limitations

- False positives can occur
- False negatives can also occur
- Severely immunocompromised patients, pregnant patients, and patients with other conditions including cystic fibrosis and prolonged infections (osteomyelitis, endocarditis, etc.) were excluded from almost all procalcitonin trials
- Procalcitonin should never override clinical judgement

Bloodstream infections

- CLABSI = central line-associated bloodstream infection
- 85,000 – 350,000 CLABSI annually in US
- Risk of bloodstream infection with central venous catheter (CVC) is ~ 2-5 per 1000 catheter days (compared with < 0.1 per 1000 catheter days for PIV)
- Exam insertion sites daily, if line does not flush or draw → concern for infection

IDSA guidelines 2008. www.idsociety.org

Blood cultures

- Technique matters:
  - clean skin with alcoholic chlorhexidine or iodine in alcohol
  - clean bottle tops with alcohol
  - draw 20-30mL of blood
  - yield optimal when 3-4 sets drawn within 24 hrs of suspected bacteremia (no best interval)
  - At least one drawn from peripheral site
- Do not routinely culture removed CVCs
- Low rate of positive results among ICU patients, but risk of missed diagnosis is high

Bloodstream infections: treatment

- Blood cultures more sensitive and specific for diagnosis of CLABSI than respiratory cultures for diagnosis of HAP/VAP
- Treatment can usually be directed by culture results
- Common bugs: **Staph aureus (MSSA, MRSA), coagulase-negative Staph**, Streptococci, GNR (including Pseudomonas), and possibly fungi…
- Line removal is optimal, but may not always be possible

Urinalysis and urine culture

- UTIs reported to be common in ICU, but no consistent definition – most studies equate isolation of bacteria/yeast with infection
- Genuine UTIs in ICU probably uncommon
- Chronic urinary catheter = chronic pyuria + bacturia
- Routine evaluation in febrile ICU patient of questionable benefit.
- Patients at high risk of complication with UTI (neutropenia, urinary obstruction, pregnancy) should have testing.
- Make sure to send both urinalysis with sediment AND urine culture

Infectious diarrhea: C Diff

- Most common cause of infectious diarrhea in hospitalized patients (especially ICU)
- May present with fever, **leukocytosis**, diarrhea
- Testing is by toxin or antigen assays of the stool (rarely with cytotoxicity assays)
- If high clinical suspicion then treat presumptively while awaiting studies
  - Oral (or rectal) vancomycin
  - IV metronidazole if severe
  - Consider surgical management

ICU-acquired meningitis? Probably not.

- 1997 study of 70 non-neurosurgical SICU patients:
  - LP performed for fever + altered mental status, as "r/o meningitis"
- No cases of meningitis discovered

- Reserve CSF exam for neurosurgical patients or severe immunocompromised

Adelson-Mitty J, et al. Intensive Care Med 1997.

Fungal infections

- Usually nosocomial (if immunocompetent)
- Invasive yeast infections:
  - Occult clinical focus and negative blood cultures in ~ 1/3 of cases
  - Risk factors: prolonged admission, underlying medical comorbid illnesses, invasive catheters, parenteral nutrition, hemodialysis, immunosuppressive therapy, and broad-spectrum antibacterials
- Mold infections: subacute presentation, often in patients with COPD and on corticosteroids

Laupland KB. Crit Care Med 2009.

Fungal isolator blood cultures?

- Not necessary
- Candida species grow well in routine blood cultures
- When evaluating for candidiasis, can consider serum 1,3-beta-D glucan testing as well
- Other serum fungal markers can be used for immunocompromised patients with fever (cryptococcal antigen, galactomannan, etc.)

Viral infections

- Most are community-acquired (influenza, parainfluenza, RSV, adenovirus, metapneumovirus, VZV, WNV…)
- Some are nosocomial reactivation of latent infections (HSV, CMV, VZV)
- Consider HIV

Laupland KB. Crit Care Med 2009.

Protozoal + parasitic infections

- Uncommon cause of fever in ICU
- Think of:
  - Malaria or babesiosis – perhaps as transfusion-associated infection
  - Anaplasma or Ehrlichia as transfusion-associated
  - Strongyloides hyperinfection syndrome in a patient from endemic area who is then treated with corticosteroids or other immunosuppressive agents

Laupland KB. Crit Care Med 2009.

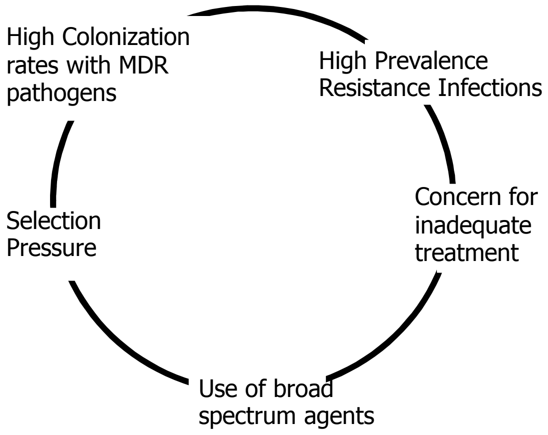
Factors encouraging antibiotic overuse in the ICU

- Unstable patients → low threshold to initiate therapy
- Pre-existing resistance → use of multiple agents
- Poor diagnostic tests → treat when no proven infection

BUT…

- Delays in adequate antimicrobial therapy in the ICU → increase mortality
  - Decreased mortality from 30% → < 15% for BSI in one study
  - Decreased mortality from > 30% → ~ 15% for HAP/VAP in other studies

Cycle of antibiotic use and resistance in the ICU



High Colonization rates with MDR pathogens

High Prevalence Resistance Infections

Concern for inadequate treatment

Use of broad spectrum agents

Selection Pressure

Antibiotic de-escalation:

- Limiting use up front is difficult.
- But subsequent actions can make significant impact:
  - Target to microbiological data
  - Discontinue as non-infectious diagnosis becomes more likely
  - Keep antibiotic courses as short as possible (eg. HAP/VAP treatment with 7 days of antibiotics)

Take home points:

- Fever in the ICU is COMMON
- Proportion of fever which is due to infection is variable but significant, likely > 50%
- Most common sites of infection are VAP and CLABSI
- Initial fever work-up should include physical exam, blood cultures, respiratory specimen culture, chest Xray, urine studies
- If bacterial infection is suspected then empiric antibiotics should be initiated after cultures have been drawn, with consideration for empiric treatment for drug-resistant organisms such as MRSA, Pseudomonas, and other resistant gram-negatives
- Broad empiric treatment is reasonable initially, but antibiotic regimens should be tailored by culture data whenever possible
- Many other causes of fever in the ICU include non-bacterial infections (eg. candidiasis, viral infections), and noninfectious causes (eg. adrenal insufficiency, drug-fever, clot, transfusion reaction…)

Review questions

Question 1

A 52 year old woman with a history of depression which is well-controlled on citalopram, as well as history of COPD (current smoker) is hospitalized with pneumonia. She requires mechanical ventilation for hypoxic respiratory failure. After intubation on admission an endotracheal tube aspirate is sent for culture and grows MRSA. She is treated with linezolid. A radial arterial catheter is placed for monitoring purposes. On hospital day #5 she develops temperature of 103.5F, as well as tachycardia and hypertension. Her ventilator requirements are unchanged.

The most likely cause of fever in this patient is:

- A. Serotonin syndrome
- B. Ventilator associated pneumonia
- C. Catheter-associated bloodstream infection with gram-negative organism
- D. C Diff infection
- E. Adrenal insufficiency

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Question 2

A 72 year old man with underlying severe interstitial lung disease is hospitalized with hypoxic respiratory failure , requires mechanical ventilation in the ICU. He has a central venous catheter placed and receives empiric treatment with for pneumonia despite absence of fever. On hospital day #4 he develops a temperature of 101.5F. Physical exam is unchanged.

Reasonable initial measures for evaluation would include all of the following except:

- A. Chest X-ray
- B. Blood cultures – 2 sets, one drawn peripherally, one from indwelling CVC
- C. Fungal isolator blood cultures
- D. Culture of endotracheal aspirate
- E. Blood liver function tests

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Question 3

A 64 year old man with a history of hepatocellular carcinoma is admitted with upper GI bleeding. He develops hypotension and is admitted to the ICU for transfusions, pressors (via CVC), and supportive care. After several maneuvers his GI bleeding stops. However, on hospital day #3 he develops fever (102.2F), and his BP drops further, pressor requirement increases. Empiric treatment with vancomycin, ceftazidime and levofloxacin is begun. On HD #4 blood cultures drawn the previous day are reported positive for MRSA.

Appropriate next steps include all of the following except:

- A. Removal of the central venous catheter
- B. Repeat blood cultures
- C. Continuation of vancomycin for at least a 14 day course
- D. Continuation of ceftazidime and levofloxacin for a 7 day course
- E. Transthoracic echocardiogram

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No conflicts of interest

Diagnosis and Management of Hyperglycemia in the ICU

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Brigham and Women's Hospital
Assistant Professor
Harvard Medical School

DISCLOSURE

Nothing to disclose

Objectives

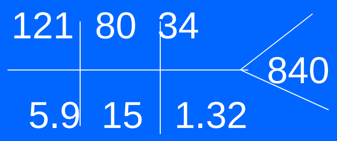
- Understand pathophysiology and diagnosis of hyperglycemic crises
- Understand components of acute treatment for hyperglycemic crises
- Review management of non-critical hyperglycemia in the ICU

Case MPN

- 71 y.o. Haitian ♀ is admitted with hyperglycemia
- Symptoms included 2-3 weeks of polyuria and polydipsia and new onset pruritic groin rash
- PMH HTN rx'd with ACE-I and Ca++ CB
- FH negative for DM
- SH neg for alcohol
- Records reveal random BG of 156 mg/dl 1 yr PTA

Case MPN

- Admission physical revealed Wt 109kg and BMI 42, candidiasis but no other infections, no MI
- Labs:



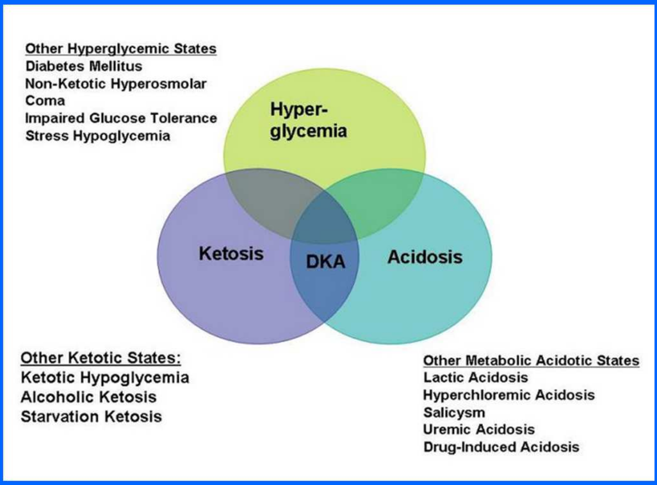
121 | 80 | 34
5.9 | 15 | 1.32
840

β-OHBT 5.18 mmol/l(nl<.3)
A1C 15.3%
Measured serum osms 311

Diagnostic Categories

- *Diabetic keto-acidosis*
  - Predominant abnormality is ketosis with acidosis in setting of hyperglycemia
- *Hyperosmolar Hyperglycemic Syndrome*
  - Predominant abnormality is dehydration due to hyperglycemia in absence of acidosis
- Insulin deficiency relative or absolute underlies these crises
- They occur in type 1 and type 2 diabetes

Overlap of Metabolic Disorders



Other Hyperglycemic States
Diabetes Mellitus
Non-Ketotic Hyperosmolar Coma
Impaired Glucose Tolerance
Stress Hypoglycemia

Other Ketotic States:
Ketotic Hypoglycemia
Alcoholic Ketosis
Starvation Ketosis

Other Metabolic Acidotic States
Lactic Acidosis
Hyperchloremic Acidosis
Salicysm
Uremic Acidosis
Drug-Induced Acidosis

Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS).
Gosmanov AR, Gosmanova EO, Kitabchi A. ***Source****Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2015 May 19.*

Diagnostic Criteria

Lab test	DKA	HHS
Glucose (mg/dl)	>250[1]	>600
Arterial pH	<7.30	>7.30
Bicarb (mEq/l)	<18	>15
Urine/Serum Ketones	Positive	Negative or trace
β–OHB(mmol/l)[2]	>3.8	<1
Effective Osmolality	variable	>320
Anion Gap	>10	variable

[1] can be lower, especially in pregnancy and with use of some medications
[2] no clear consensus

Adapted from Kitabchi et al DC 32:1335, 2009

Degrees of DKA

- "MILD DKA" is Bicarb 15-18 and arterial pH 7.25-7.3, normal mental status
- "MODERATE DKA" is Bicarb 10-14 with pH 7.0-7.24, alert or drowsy mental status
- "SEVERE DKA" is Bicarb <10 or with <pH 7.0, stupor or coma

Serum bicarbonate levels may underestimate bicarbonate deficit in severe volume contraction and may drop with fluid expansion

NEJM 372:546, 2015

Pathogenesis of DKA/HHS

- Insulin target tissues
  - Liver
  - Muscle
  - Adipose tissue
- Insulin Action
  - Decrease glucose production
  - Increase glucose uptake
  - Decrease lipolysis
  - Less insulin(1/10) needed to suppress lipolysis than to suppress gluconeogenesis

Pathogenesis of DKA/HHS

- “Counter-regulatory” hormones
  - Glucagon
  - Epinephrine
  - Cortisol
  - Growth hormone
- Counter-regulatory hormones antagonize insulin effects on glucose/free fatty acid levels
- Glucagon levels rise when insulin is absent

Pathogenesis of DKA/HHS

- Dehydration occurs when hyperglycemia promotes osmotic diuresis and fluid intake is inadequate to keep up with losses
  - Immobility, dementia, diuretics, gastrointestinal illness
- Ketosis occurs when insulin is low and counter-regulatory hormones are elevated
  - Free fatty acids are metabolized to “ketone bodies” acetone, aceto-acetate,and β-oh butyrate

Epidemiology

- DKA estimated to account for 140,000 hospitalizations in US and 500,000 hospital days
- HHS less common but higher mortality
- Mortality has been decreasing with improved management

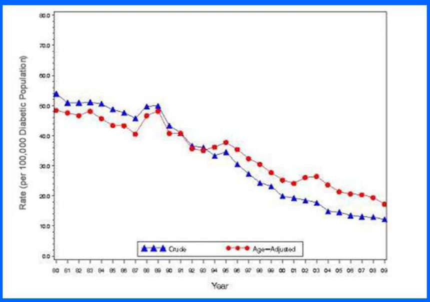


Figure 1b Crude and Age-Adjusted Death Rates for Hyperglycemic Crises as Underlying Cause per 100,000 Diabetic Population, United States, 1980–2009

Precipitating Factors for DKA/HHS

- New onset diabetes 50%
- Medication non-compliance 25%
- Infection 20-25%
- Cardiovascular event 2-5%
- Pancreatitis 5%
- New drugs: steroids, newer anti-psychotics
- Substance abuse co-exists in 25-50%

Clinical Features

Dehydration symptoms:

- Polyuria, polydipsia,
- Fatigue
- Dry mucus membranes
- Hypotension
- Neurologic symptoms including focal abnormalities, seizures and lethargy and coma

Keto-Acidosis Symptoms:

- Abdominal pain, nausea, vomiting(should be aggressively investigated in absence of ketoacidosis)
- Rapid, deep and labored breathing
- “Fruity” breath

Initial Labs to Order

- Plasma glucose(actual measured)
- BUN, creatinine, electrolytes
- Serum ketones and urine ketones
- ABG
- Osmolality
- CBC
- Any indicated labs or imaging to determine cause

Handy Formulas

1. Anion Gap: Normal ~ 10-16
   Na – (HCO3 + Cl)
   Our patient: 121 – (15 + 80) = 26

2. Effective serum osmolality: Normal 275-299 2[measured Na(meq/l)] + glucose(mg/dl)/18
   Our patient: 2(121) + 840/18 = 289

3. Osmolal gap is: measured osms - calculated osms(effective osms + BUN/2.8)
   Our patient 311-301 = 10 normal osmolal gap 2-3

4. "Corrected Na": Normal 135-145
   Na(measured) + .024X[glucose(mg/dl) - 100]
   corrected Na helps put measured Na in context when glucose very high
   Our patient: 121 + .024(740) = 139

Laboratory Pitfalls

- Lipase levels can be falsely elevated if the assay measures glycerol which can be very elevated in DKA
- Creatinine can be falsely elevated by ketones if a colorimetric method is used
- Nitroprusside reactions for ketone bodies will not detect β-oh butyrate(earliest ketone to appear) so this must be ordered separately if available

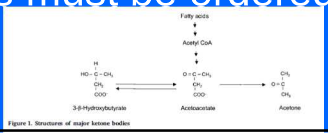
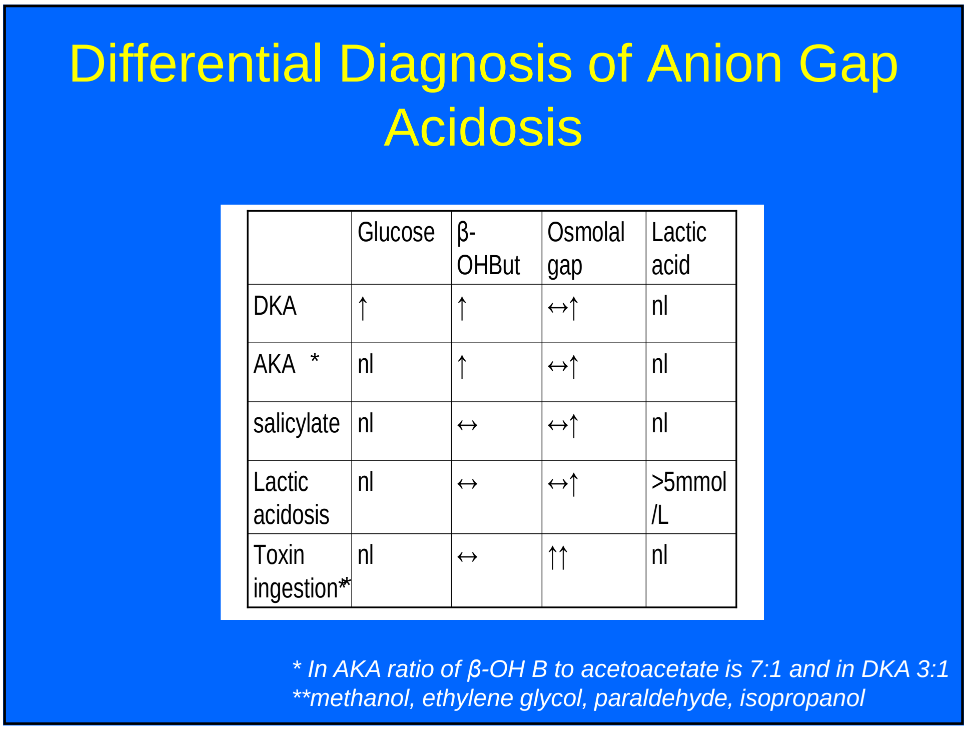

Fatty acids
Acetyl CoA
HO – C – CH₃
H
CH₂
COO⁻
O = C – CH₃
CH₂
COO⁻
CH₃
O = C
CH₃
3-β-Hydroxybutyrate
Acetoacetate
Acetone

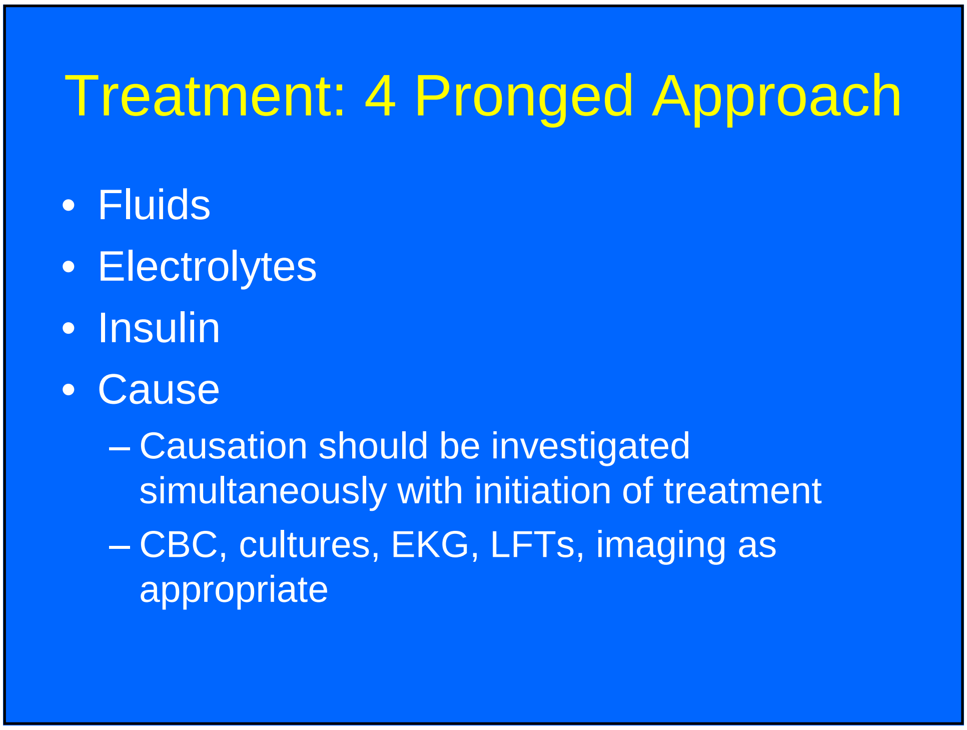
Figure 1. Structures of major ketone bodies



Differential Diagnosis of Anion Gap Acidosis

	Glucose	β-OHBut	Osmolal gap	Lactic acid
DKA	↑	↑	↔↑	nl
AKA *	nl	↑	↔↑	nl
salicylate	nl	↔	↔↑	nl
Lactic acidosis	nl	↔	↔↑	>5mmol /L
Toxin ingestion**	nl	↔	↑↑	nl

** In AKA ratio of β-OH B to acetoacetate is 7:1 and in DKA 3:1*
***methanol, ethylene glycol, paraldehyde, isopropanol*



Treatment: 4 Pronged Approach

- Fluids
- Electrolytes
- Insulin
- Cause
  - Causation should be investigated simultaneously with initiation of treatment
  - CBC, cultures, EKG, LFTs, imaging as appropriate

Treatment of DKA/HHS: Fluids

- Fluid deficits can be substantial
  - DKA up to 3-5 liters
  - HHS 5-9 liters
- Fluids should initially be replaced with normal saline
  - 1 liter/hour or 15-20 ml/kg/hour for at least 1 hour
- Use caution in CHF and ESRD

Treatment of DKA/HHS: Fluids

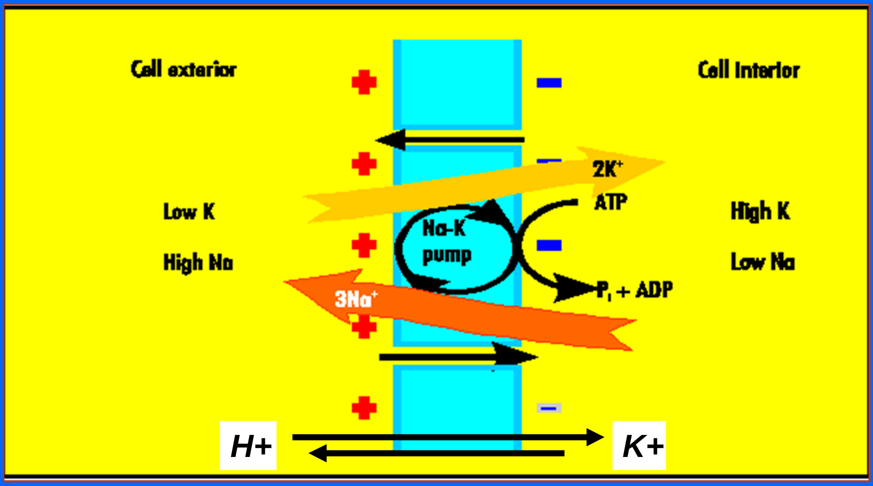
- Restore plasma volume with normal saline
  - Blood pressure normalized
  - Urine output improved(50 cc/hour)
- Subsequent fluid choice based on cNa+
  - Use .45% Na if cNa+ is > 135 meq/l
  - Use .9% Na if cNa+ is ≤ 135 meq/l
- In HHS rapid correction of hyperosmolarity is not recommended so transition to hypotonic solution should be conservative
- Add dextrose when glucose reaches 200-250mg/dl(DKA) or 300mg/dl(HHS)

Fluid replacement in children

- Cerebral edema is a rare complication of DKA in children
- Large initial volumes of fluid have been associated with an increase in risk
- Suggested response: avoid decrease in effective plasma osmolality for first 15 hours of treatment through continued use of normal saline

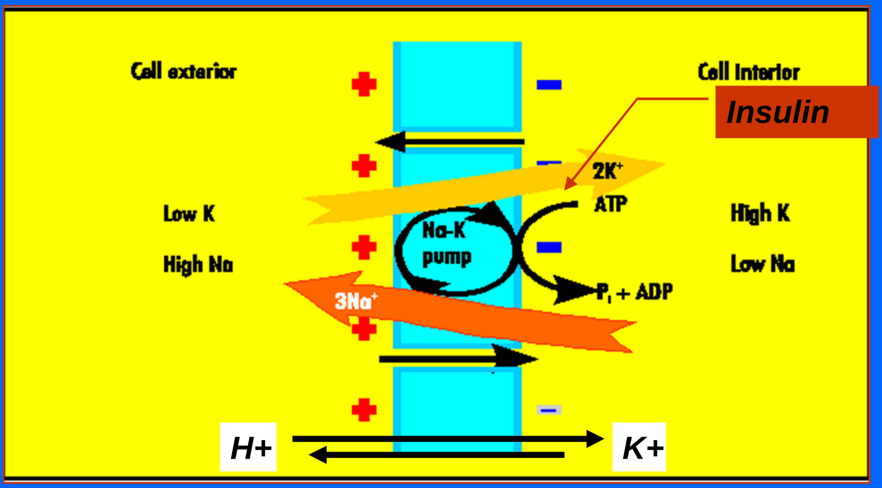
NEJM 372:546, 2015

Treatment of DKA/HHS: Potassium


Cell exterior
Cell interior
2K+
ATP
Low K
High Na
Na-K pump
High K
Low Na
P$_i$ + ADP
3Na+
H+
K+

Graphic courtesy of M McDonnell

Treatment of DKA/HHS: Potassium


Cell exterior
Cell Interior
Insulin
2K⁺
ATP
Low K
High Na
Na-K pump
High K
Low Na
Pᵢ + ADP
3Na⁺
H+
K+

Graphic courtesy of M McDonnell

Treatment of DKA/HHS: Potassium

- Insulin and sodium bicarbonate can lower potassium significantly
- Never administer insulin or bicarbonate until potassium level is available
- Assume potassium depletion exists except in ESRD
- Fluids will help to lower glucose initially

Treatment of DKA/HHS: Potassium

–If K+ is 3.3- 5.2 mEq/L give 20-30 mEq K+ (as KCl) per liter in iv fluids

–If K+ is < 3.3 mEq/L

- Give KCl 20-30 mEq/hour iv centrally and monitor in ICU
- Hold insulin until K+ is ≥ 3.3meq/L

–Goal for K+ is maintenance at 4-5 mEq/L

–Use caution in patients with significant renal impairment

Treatment of DKA/HHS: Bicarb and Phosphate

- Bicarbonate
  - In general, supplementation with bicarbonate is not necessary and may worsen hypokalemia
  - Consider supplementation if pH ≤6.9
- Phosphate
  - Insulin and fluid replacement will lower phosphate
  - Replacement not necessary unless phosphate<1.0 mg/dl
  - Milk is a good source of phosphate when patient is eating

Treatment of DKA/HHS: Insulin

- iv regular insulin therapy is preferred to sc in ICU
- Initial dose:
  - .1 U/kg as bolus and .1 U/kg/hr drip
  - Bolus can be repeated X1 if glucose doesn't drop after 1 hour
  - No bolus if hypokalemic at presentation or for children
- Adjust drip as needed to lower glucose 50-75 mg/dl/hour
- Check glucose hourly at least initially
- Target glucose level
  - DKA 150-200 mg/dl
  - HHS 200-300 mg/dl

What About sc Insulin?

- Subcutaneous regimens are available for mild to moderate DKA
  - Start .2 units/kg rapid acting analog insulin
  - Then 0.1 units/kg/hour or 0.2 units/kg/ 2 hours until BG<250
  - Cut dose in half until episode is resolved
- Do not use in severe or complicated DKA or HHS

Treatment of DKA/HHS: Transition to sc insulin

- Patient should be clinically stable and able to eat
- Resolution of episode by laboratory tests
  - DKA
    - Glucose <200mg/dl and 2 of 3: bicarbonate>15 mEq/l, venous pH >7.3, AG<12
    - NaCl containing fluids can lead to a phase of hyperchloremic acidosis with no AG
  - HHS
    - Serum osms <315 and baseline mental status

Treatment of DKA/HHS

- Transition to sc
  - Calculate total daily dose: 0.5 units/kg/day split 50% basal and 50% divided among meals(weight based method)
  - Continue insulin drip for *at least* 2 hours after initial sc insulin dose given (give rapid acting and basal)
  - Correctional insulin(sliding scale) to start after drip stopped
  - Patients with established insulin doses can be restarted as appropriate

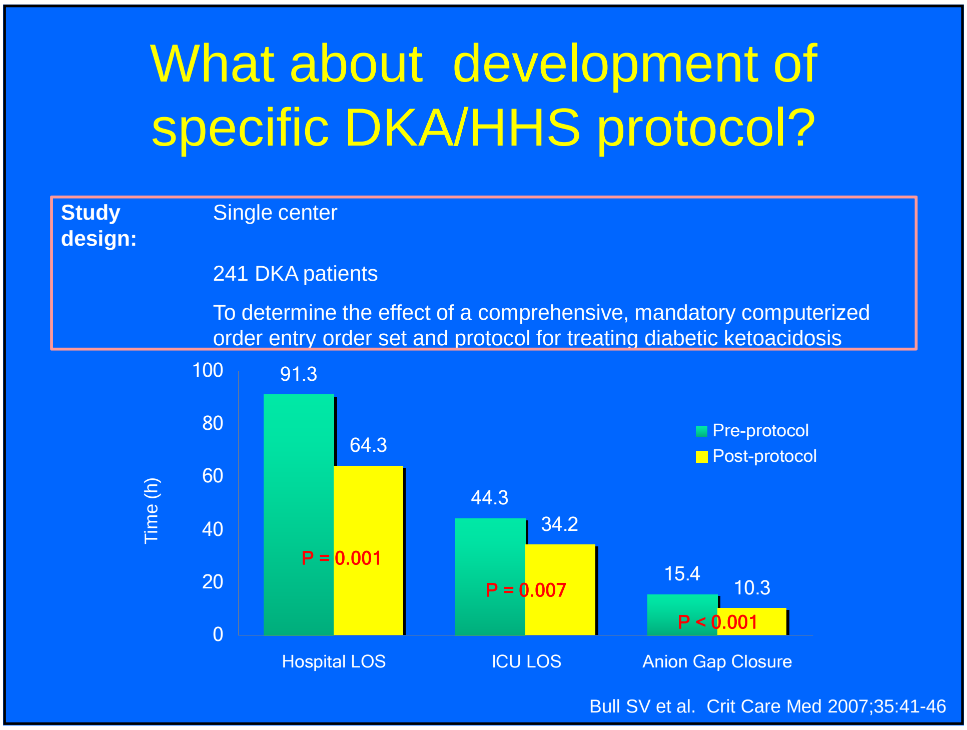
Improving transition to sc from iv insulin

- Recent study randomized 60 patients on iv insulin to “early”(within 12 hours of starting drip) basal insulin or conventional insulin (2 hours prior to stopping iv insulin) in patients with DKA, post-op, or high dose steroids
- Intervention patients received .25 units/kg/day basal insulin in addition to iv insulin
- Post-transition 33% of intervention group had rebound hyperglycemia compared to 90% of conventionally treated group

J Clin Endocrinol Metab, September 2012, 97(9):3132–3137

Treatment of DKA/HHS:Complications

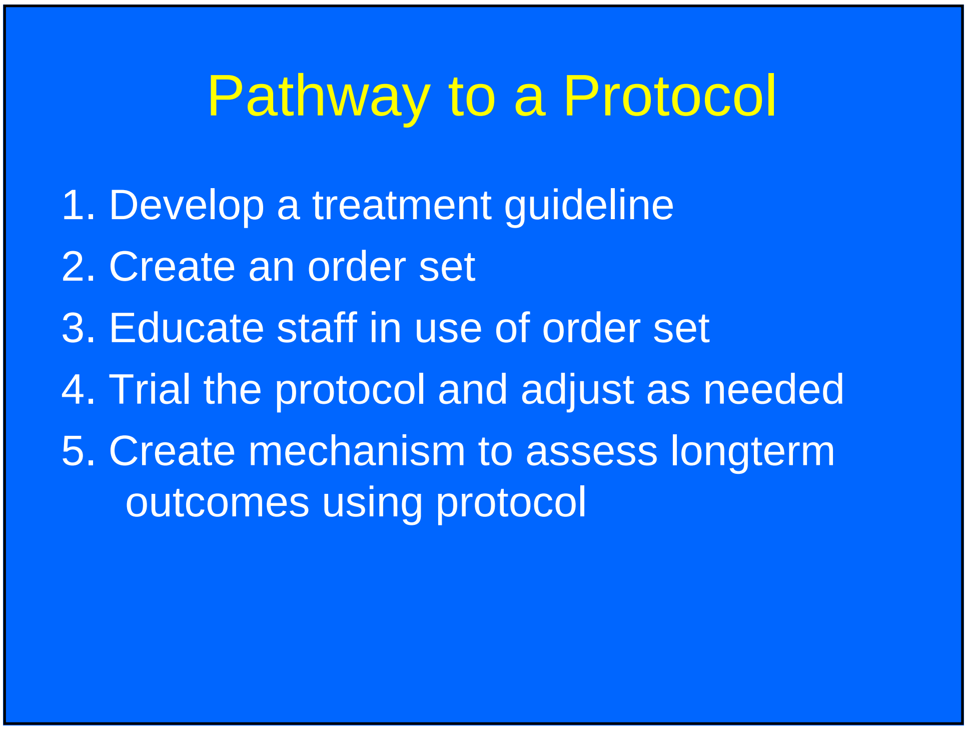
- Hypokalemia can be dangerous
- Hypoglycemia is avoidable with adequate monitoring
- Hypophosphatemia usually does not require treatment
- Cerebral edema occurs in up to 1% of children but is rare in adults
  - Actual cause not known
  - Avoid rapid lowering of plasma osmolality
  - Mortality up to 70%



What about development of specific DKA/HHS protocol?

Study design:	Single center
	241 DKA patients
	To determine the effect of a comprehensive, mandatory computerized order entry order set and protocol for treating diabetic ketoacidosis

Bull SV et al. Crit Care Med 2007;35:41-46



Pathway to a Protocol

1. Develop a treatment guideline
2. Create an order set
3. Educate staff in use of order set
4. Trial the protocol and adjust as needed
5. Create mechanism to assess longterm outcomes using protocol

Back to our patient

- She was treated with iv fluids, iv insulin bolus and insulin drip and potassium
- She was transitioned to sc insulin and discharged
- Within 2 months she was on metformin alone
- 30% of African-American or Hispanic patients with DKA have type 2 diabetes

Changing Gears

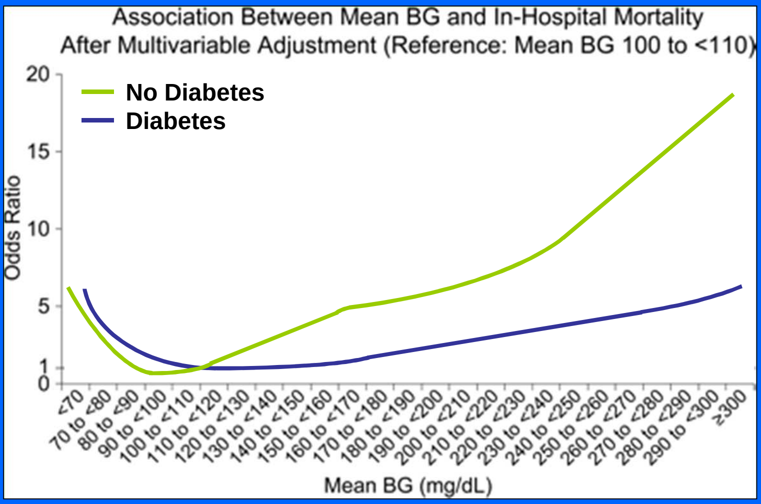
Management of non-critical hyperglycemia in the ICU

Definition of terms

- Hospital hyperglycemia: Any BG > 140 mg/dl (7.8 mmol/L)
- Stress hyperglycemia: Elevations in blood glucose levels that occur in patients with no prior history of diabetes and A1c levels that are not significantly elevated (<6.5%)
- A1c values equal to or above 6.5% in patients with hyperglycemia suggests a prior history of diabetes
- Hypoglycemia: Any BG < 70 mg/dl (3.9 mmol/L)
- Severe hypoglycemia:
  - Any BG < 40 mg/dl (2.2 mmol/L)(older criteria)
  - <54 mg/dl "serious" newer criteria
  - Cognitive impairment with any value glucose below 70

ADA Standards of Care 2017

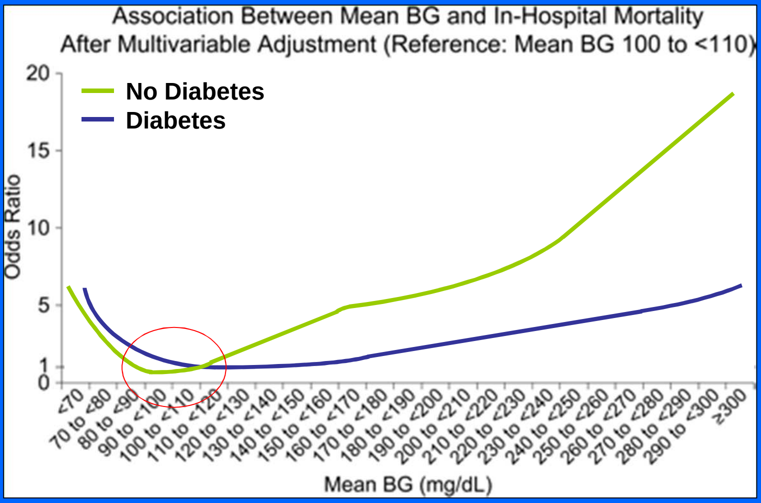
Why Control Glucose Levels?



Kosiborod et al Circulation 117:1018-1027, 2008

Evaluation of 16,000 admissions for MI

Why Control Glucose Levels?



Association Between Mean BG and In-Hospital Mortality
After Multivariable Adjustment (Reference: Mean BG 100 to <110)

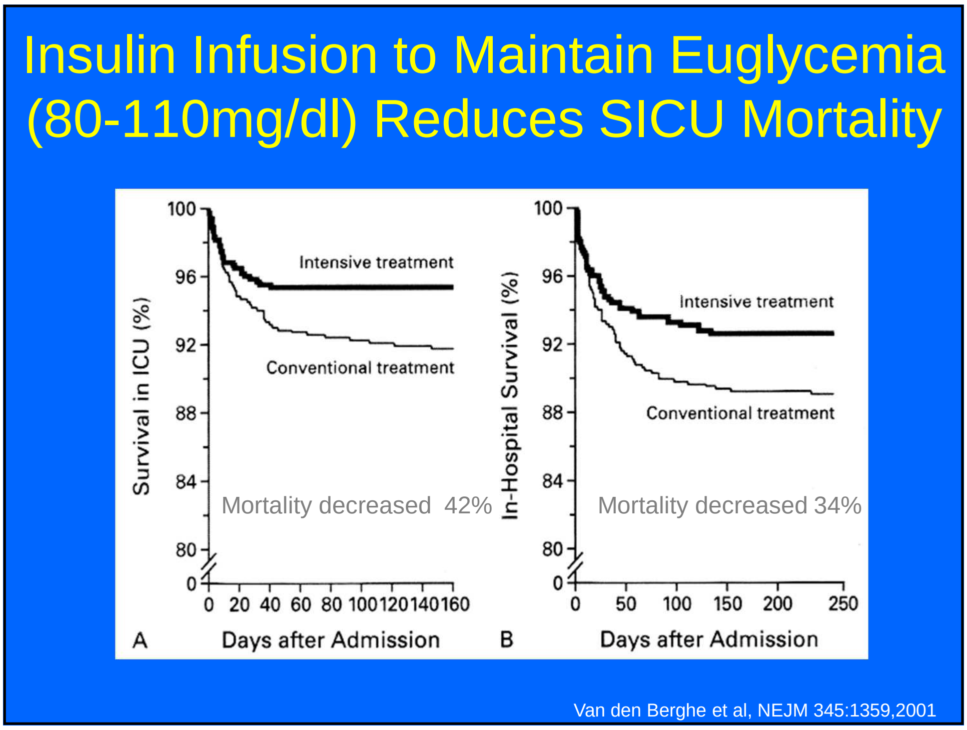
Kosiborod et al Circulation 117:1018-1027, 2008

Evaluation of 16,000 admissions for MI

Link Between High Blood Glucose and Poor Outcomes: Potential Mechanisms

- Metabolic stress increases counter-regulatory hormones
- This leads to increase in glucose, lactate and free fatty acids
- Metabolic changes contribute to
  - Immune dysfunction
  - Increase in reactive oxygen species
- Ultimate effect is poor healing, increase in apoptosis and tissue damage

Diabetes Care 2004;27:553–591

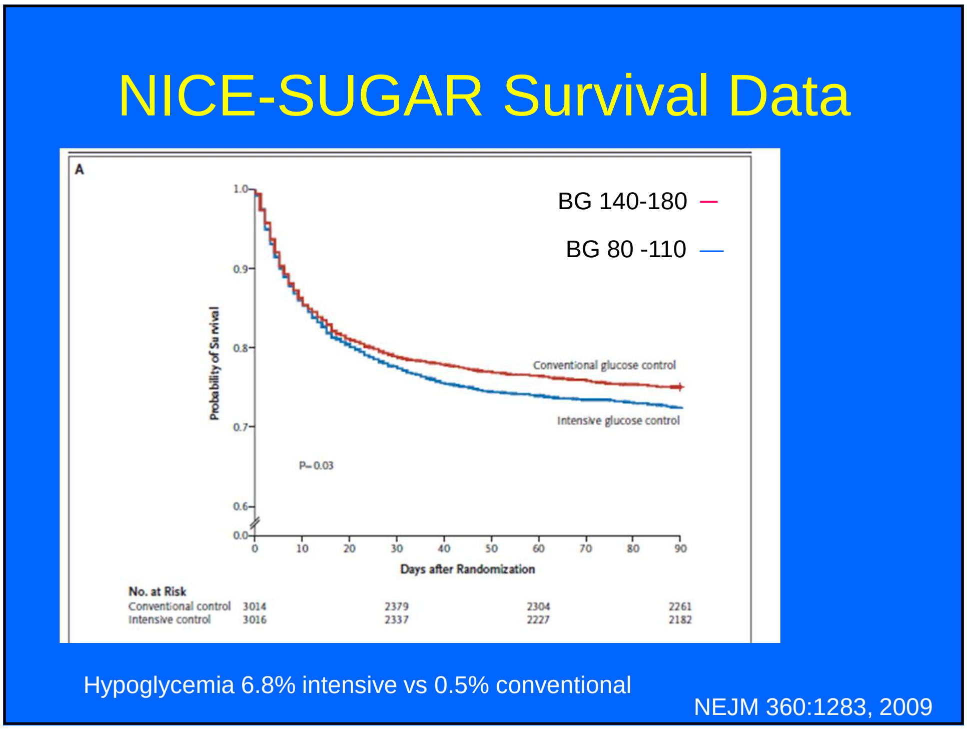


Insulin Infusion to Maintain Euglycemia (80-110mg/dl) Reduces SICU Mortality

Mortality decreased 42%

Mortality decreased 34%

Van den Berghe et al, NEJM 345:1359,2001



NICE-SUGAR Survival Data

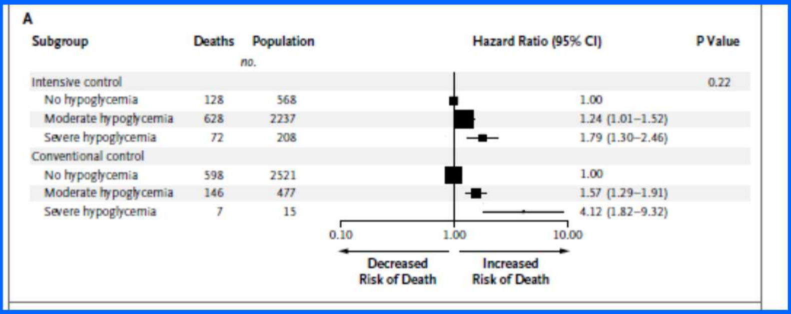
No. at Risk

Conventional control	3014	2379	2304	2261
Intensive control	3016	2337	2227	2182

Hypoglycemia 6.8% intensive vs 0.5% conventional

NEJM 360:1283, 2009

Mortality and hypoglycemia in NICE-SUGAR



A

Subgroup	Deaths	Population	Hazard Ratio (95% CI)	P Value
		no.		
Intensive control				0.22
No hypoglycemia	128	568	1.00	
Moderate hypoglycemia	628	2237	1.24 (1.01–1.52)	
Severe hypoglycemia	72	208	1.79 (1.30–2.46)	
Conventional control				
No hypoglycemia	598	2521	1.00	
Moderate hypoglycemia	146	477	1.57 (1.29–1.91)	
Severe hypoglycemia	7	15	4.12 (1.82–9.32)	

NEJM 367:1108, 2012

AACE/ADA recommended target glucose levels in the ICU

- **ICU setting:**
  - Starting threshold of no higher than 180 mg/dLfor iv insulin infusion
  - Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL
  - Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients
  - Targets <110 mg/dL or >180 mg/dL are not recommended

Not recommended <110	Acceptable 110-140	Recommended 140-180	Not recommended >180

Moghissi ES, et al; AACE/ADA Inpatient Glycemic Control Consensus Panel. *Endocr Pract.* 2009;15(4).

Insulin Infusion Protocol:Advantages

- Useful for covering basal requirements
- Maintains glucose in a pre-specified range
- Able to be easily adjusted as patient needs change
- Most protocols are equivalent in results as long as nursing is adequately trained
- Low risk of hypoglycemia with higher goals

Insulin Infusion Protocol: Disadvantages

- Technically difficult requiring intensive nursing and hourly glucose values
- Does not address prandial (intermittent feeding)needs of the patient
  - If patient is stable transition to sc insulin and stop drip
  - If patient is not stable add sc analog insulin ac to prevent excursions
- Must be transitioned to another form of insulin delivery for long term glucose management

New Controversy: POC Glucose Testing in the ICU

- POC testing with conventional glucose meters in "critically ill patients" is not FDA approved use of the technology
- Federal Government agencies may move to require further testing in ICUs for approval for routine use
- Critical illness not defined

What are some of the issues?

- Accuracy
  - POC testing in general
    - Current meters are required to prove 95% of values are within 20% of reference (ISO standard)
    - In outpatient setting 99% of values are within 20% and median difference from reference is 5%
  - Blood gas analyzers are more accurate but require arterial line
- Arterial glucose > capillary glucose > central venous glucose
  - in hypotension decreased perfusion leads to increased glucose utilization and greater difference between arterial and venous glucose

Known sources of inaccuracy in POC testing

- Extremes of hematocrit
  - < 20% overestimates glucose
  - >70% underestimates glucose
- Triglycerides > 1500 mg/dl lowers glucose
- Bilirubin > 40 mg/dl
- Uric Acid > 23.5 mg/dl
- pH <6.95
- Hypothermia: false lows

Known sources of inaccuracy in POC testing

Acetaminophen > 20mg/dl raises glucose

Ascorbic acid >5 mg/dl falsely lowers

Non-glucose sugars that may falsely elevate glucose depending on the type of meter

Maltose

Galactose

Icodextrin peritoneal fluid

Mannitol

Dopamine falsely increases levels

Summary

- DKA and HHS may have significant overlap in laboratory findings
- Treatment should proceed on several fronts simultaneously
- Protocols may help improve outcomes and standardize care
- Goals for glucose in the ICU have been evolving
- Hypoglycemia is associated with increase in mortality
- POC testing may be impacted by conditions common in the ICU

Question 1

- Initial management of DKA or HHS usually includes which of the following:

  A) 0.45% saline infusion

  B) iv insulin bolus of 0.2 units/kg body weight

  C) 2 amps sodium bicarb in 400 ml sterile water iv over 2 hours

  D) Search for precipitating cause

Question 1

- Initial management of DKA or HHS usually includes which of the following:
  - A) 0.45% saline infusion
  - B) iv insulin bolus of 0.2 units/kg body weight
  - C) 2 amps sodium bicarb in 400 ml sterile water iv over 2 hours
  - ***D) Search for precipitating cause***

Question 2

- Which of the following are not complications of treatment for DKA or HHS
- A) Hypokalemia
- B) Renal insufficiency
- C) Hypoglycemia
- D) Hypophosphatemia
- E) Hyperchloremic acidosis

Question 2

- Which of the following are not complications of treatment for DKA or HHS
- A) Hypokalemia
- ***B) Renal insufficiency***
- C) Hypoglycemia
- D) Hypophosphatemia
- E) Hyperchloremic acidosis

Question 3

- Stress hyperglycemia is:
  - A) Associated with increased mortality in patients with MI
  - B) Seen in patients with A1C levels over 6.5%
  - C) Usually treated with metformin
  - D) A permanent condition
  - E) Indicated by a glucose > 110 mg/dl

Question 3

- Stress hyperglycemia is:
  - A) Associated with increased mortality in patients with MI
  - B) Seen in patients with A1C levels over 6.5%
  - C) Usually treated with metformin
  - D) A permanent condition
  - E) Indicated by a glucose > 110 mg/dl

Selected References

- Moghissi ES et al American Association of Clinical E, American Diabetes A. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes care.* Jun 2009;32(6):1119-1131.
- Gosmanov A, Gosmanova E, Kitabchi A Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS). In: http://www.endotext.org/diabetes/diabetes24/diabetesframe24.htm update 2015
- NICE-SUGAR Study investigators Intensive vs conventional glucose control in critically ill patients NEJM 360:1283, 2009.

DISCLOSURE

No Disclosures

End slide

- Word Document Post-test question Hyperglycemic Emergencies
- A 57 year old woman with known type 2 diabetes presents to the ER with 4 days of abdominal pain, nausea and vomiting. Physical exam significant for temperature of 100^0F, BP of 90/60 P 100 and her abdomen is distended. Laboratory studies show the following:
- Na 117 mmol/L K 4.6 mmol/L Cl 93 mmol/L CO2 8 mmol/L
- BUN 49 mg/dl Cr 1.57 mg/dl
- Glucose 1084 mg/dl
- Measured serum osmolality is 324 mOsm/kg
- β–OHB 0.7 mmol/l
- Lactic acid 10.2 mmol/L
- ABG pH 7.10
-
- Her most likely diagnosis(diagnoses) include(s) which of the following explanations for her laboratory abnormalities:
- A. Severe hyponatremia
- B. Diabetic keto-acidosis
- C. Lactic acidosis
- D. Hyperosmolar hyperglycemic syndrome
- Answer: C and D
- Explanation:
- She does not have significant hyponatremia because the corrected sodium is 117 + 1084X.024 which is 143 mmol/l. Her mild elevation of beta-hydroxybutyrate does not account for the profound acidosis and is common in patients who haven't been eating recently so she does not have diabetic ketoacidosis. Her lactate level is consistent with a diagnosis of lactic acidosis, being over 5 mmol/l.
- Does she meet criteria for HHS? Her effective serum osms are 2X117 + 1084/18 which is 294 so not strictly hyperosmolar (normal up to 295 by most labs) by this criteria. However her measured serum osmolality is 324(clearly hyperosmolar). Is there an osmolal gap? Calculated osmolality would include BUN/2.8 so the value would be 294 + 17 which equals 311 showing an osmolal gap(324-311=13). This gap is most likely due to the lactic acid.
- Because of physical findings and suggestive laboratory studies a secondary cause of her hyperglycemia and acidosis was sought and a perforated viscus was discovered. Treatment involved fluid resuscitation, insulin drip and surgery. In the final analysis, she has an overlap syndrome with both lactic acidosis and severe hyperglycemia and dehydration.

Board Review Question

- 57 yr old ♀ with known type 2 DM presents to ER with 4 days abd pain, nausea and vomiting
- Temp is 100 and abd is distended
- Labs: Na 117 mmol/L K 4.6 mmol/L

  Cl 93 mmol/L CO2 8 mmol/L BUN 49 mg/dl Cr 1.57 mg/dl Glucose 1084 mg/dl
- Measured serum osms 324
- β–OHB mmol/l 0.7
- Lactic acid 10.2 mmol/L

What does she have?

- A. Severe hyponatremia
- B. Diabetic keto-acidosis
- C. Lactic acidosis
- D. Hyperosmolar hyperglycemic syndrome
- E. Combination of 2

Answer

- A. Severe hyponatremia
- B. Diabetic keto-acidosis
- C. Lactic acidosis
- D. Hyperosmolar hyperglycemic syndrome
- E. Combination C and D
  - Corrected sodium is 141 meq/L so this is not A
  - β–OHB is not high enough for ketones to be accounting for acidosis so this is not DKA
  - Lactic acid level is high enough to account for acidosis
  - Elevated glucose and measured serum osms high enough to meet criteria for HHS

Treatment

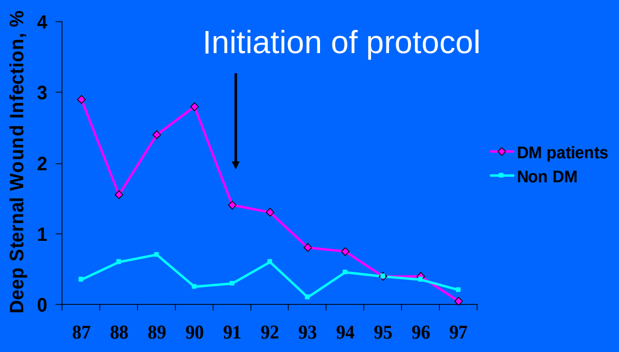
- Look for cause of lactic acidosis: perforated duodenal ulcer
- Provide fluid resuscitation with normal saline
- Start iv insulin drip
- Watch K closely (it dropped to 3.0 with fluids in 2 hours!)

End of Discussion

Why not use standard ICU iv insulin protocol?

- Usual iv insulin protocols do not include provisions for fluid and electrolyte replacement
- Glucose goals for iv insulin protocols are lower than recommended in hyperglycemic crises
- Standard ICU protocols may discontinue iv insulin too soon

Insulin Infusion Protocol Reduces Rates of Wound infections



DSWI rate decreased 3.8% to .8%

Furnary AP, Starr A et al, 1999, Ann Thor Surg 67:352-62

Euglycemic IV Insulin Protocols in MICU

- Mortality benefit only in patients with longer ICU stays
- High frequency of severe hypoglycemia: 18% intensive protocol vs 3% conventional protocol had at least one BG < 40 mg/dl

Van den Breghe, NEJM 2006;354, 449

Common Problems with IV Insulin Protocols

- How high can dose go?
  - When high rates (over 10-20 units/hour) are required look for a cause
    - IV has infiltrated
    - Pressors or steroids are in use
    - New problem has developed such as undiagnosed sepsis
  - Rates over 60 units/hour are rarely required
    - Patients usually with very poor perfusion and insulin has no where to “act”
    - Drip rate itself becomes a source of excess fluid
    - Limits on D5W in fluids helpful

Suitability of Arterial Blood Glucose Analysis In Patients Receiving Vasopressors

Zone A= ISO met

Zone B = not met but no expected clinical decision difference

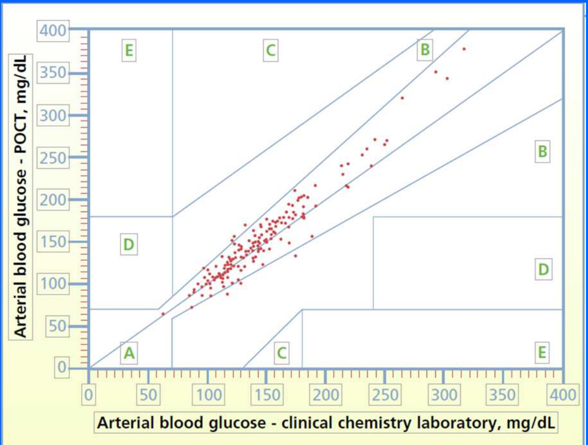


Figure 2 Accuracy of arterial point-of-care testing versus clinical chemistry laboratory testing for measurement of blood glucose levels (N = 126).

American Journal of Critical Care. 2013;22:423-430

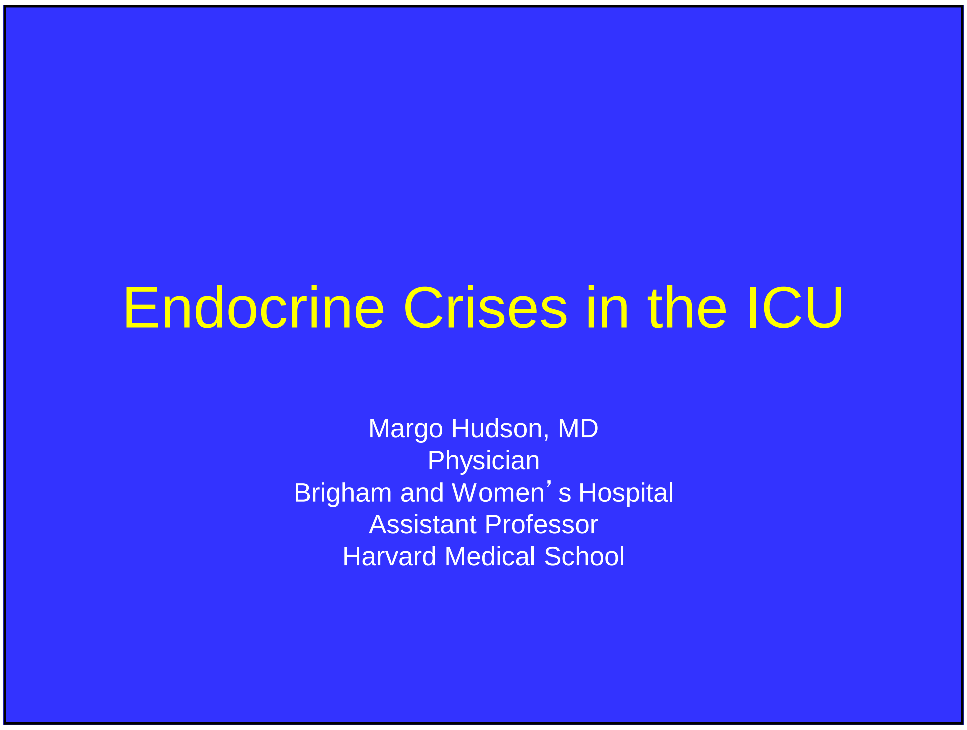
Epidemiology of DKA/HHS

- Admissions for DKA up 35% in past decade
- 30% of African-American or Hispanic adults with DKA have type 2 diabetes
- Mortality improving but remains significant
  - >5% in elderly with DKA
  - Up to 20% in elderly with HHS

Adapted from Kitabchi et al DC 32:1335, 2009

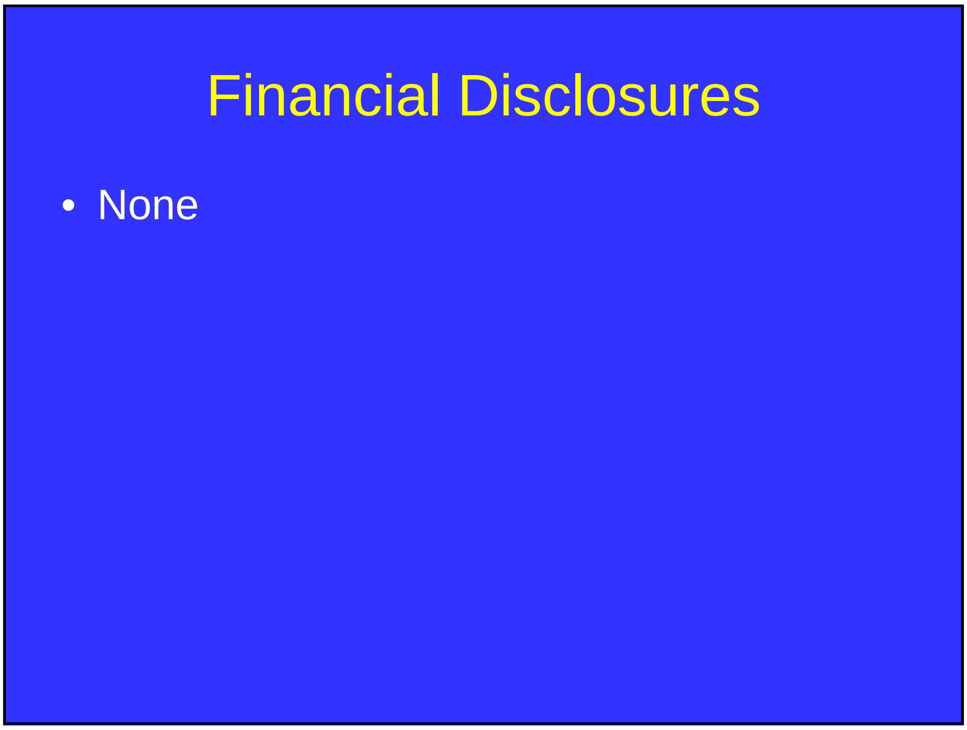
Common Problems with IV Insulin Protocols

- The patient is eating and gets hyperglycemic on the protocol
- Solution:
  - If patient is stable transition to sc insulin and stop drip
  - If patient is not stable add sc analog insulin ac to prevent excursions



Endocrine Crises in the ICU

Margo Hudson, MD
Physician
Brigham and Women's Hospital
Assistant Professor
Harvard Medical School



Financial Disclosures

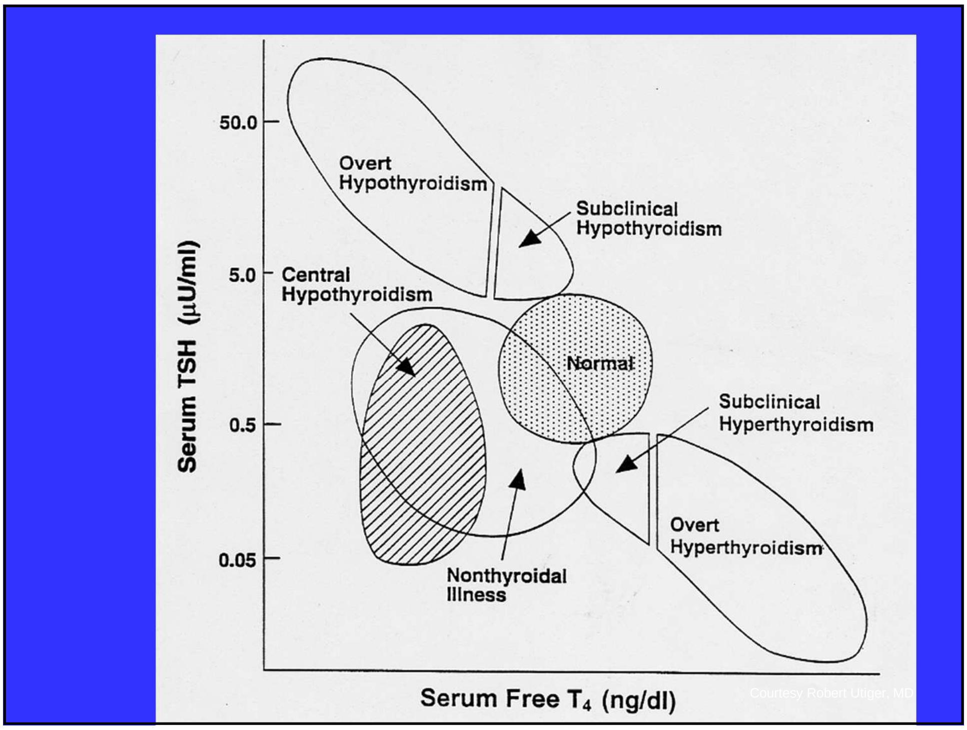
- None

Outline

- Thyroid Storm
- Amiodarone-induced thyrotoxicosis
- Myxedema coma
- Adrenal insufficiency
- Hypercalcemia

Thyroid Function Tests in the ICU

Diagnosis	TSH	Free T4	Total T3
1° Hyperthyroidism	↓↓↓	↑	↑
1° Hypothyroidism	↑	↓	↔↓
2° Hypothyroidsm	↔↓	↓	↔↓
Non-thyroidal illness	↔↓	↔↓	↓↓↓


Serum TSH (µU/ml)
50.0
5.0
0.5
0.05
Overt Hypothyroidism
Subclinical Hypothyroidism
Central Hypothyroidism
Normal
Subclinical Hyperthyroidism
Overt Hyperthyroidism
Nonthyroidal Illness
Serum Free T4 (ng/dl)

Courtesy Robert Utiger, MD

Drugs Causing Changes in Thyroid Hormones

- Suppress TSH
  - Dopamine
  - High dose steroids(acutely)
- Cause 1° hypothyroidism
  - Lithium
- Cause hypo and hyperthyroidism
  - Amiodarone
- Falsely elevate thyroid function tests
  - Biotin

Accelerated Hyperthyroidism aka Thyroid Storm: Criteria

- Clinical features:
  - Fever
  - Gastrointestinal symptoms/ jaundice
  - Tachycardia and/or atrial fibrillation
  - CHF
  - Restlessness, delirium, psychosis and eventually stupor, seizures, and coma
- Laboratory features
  - No laboratory features distinguish thyroid storm from usual hyperthyroidism
  - LFT abnormalities, hyperglycemia, hypercalcemia, azotemia may be present
- Burch-Wartofsky Point scale available for diagnosis (over 45 consistent with diagnosis)

Endocrinol Metab Clin North Am. 1993; 22:263-277.

Accelerated Hyperthyroidism aka Thyroid Storm

- Over 90% of patients have Graves' disease
- Mortality remains a problem: 8% in recent series
- Precipitants
  - Infection
  - Surgery
  - I 131 treatment or contrast exposure
  - Abrupt cessation of anti-thyroid medication
  - Toxemia

Endocrine Practice 17:457, 2011
JCEM 100:451, 2015

Accelerated Hyperthyroidism aka Thyroid Storm: Treatment

- Patient should be monitored in ICU setting
- Initiate treatment with anti-thyroid medications
  - Inhibit production of thyroid hormone by inhibiting organification of iodide (thionamide)
  - PTU vs methimazole
    - preferred over methimazole because of inhibition of peripheral conversion of T4 to T3
    - dosing 500-1000mg loading dose then 200 mg q 4
    - Concerns for liver dysfunction with PTU chronically

Accelerated Hyperthyroidism aka Thyroid Storm: Treatment

- Administer iodine
  - Iodine blocks release of pre-formed thyroid hormone
  - If possible start after initial dose of PTU is given
  - Start SSKI 5 drops q 6 hour
- Administer corticosteroids
  - Will suppress thyroiditis if present
  - Decrease T4 to T3 conversion, and support stress response
  - Dose 8 mg qd dexamethasone or hydrocortisone 300mg iv and then 100mg iv q 8
- Administer beta-blocker
  - This will slow tachycardia
  - Decreases T4 to T3 conversion
  - Use propranolol 60-80 mg q 4 h or esmolol infusion
  - If beta-blockers are contra-indicated consider diltiazem

Accelerated Hyperthyroidism aka Thyroid Storm: Treatment

- Supportive measures
  - Acetaminophen is preferred over salicylates for pyrexia: asa ↑ free hormone levels
  - Avoid external cooling as shivering may raise temperature
  - Correct dehydration
  - Cautious treatment of heart failure with diuretics if necessary
- When all else fails: case reports
  - Plasmapheresis or dialysis
  - Cholestyramine

Amiodarone-induced Thyrotoxicosis (AIT)

- Patients are ***ill*** from cardiac and thyroid conditions
- 10% mortality reported
- Most AIT in US is due to ***thyroiditis***(destruction) not ***hyperthyroidism(excess synthesis)***
- ***Doppler study of thyroid*** may distinguish hyperthyroidism from thyroiditis
- ***Steroids*** are most effective in thyroiditis form
- ***Methimazole*** 40 mg qd is used if hyperthyroidism present
- Iodine is ***ineffective***
- ***Perchlorate*** suggested but not available in US
- ***Surgery*** may need to be considered

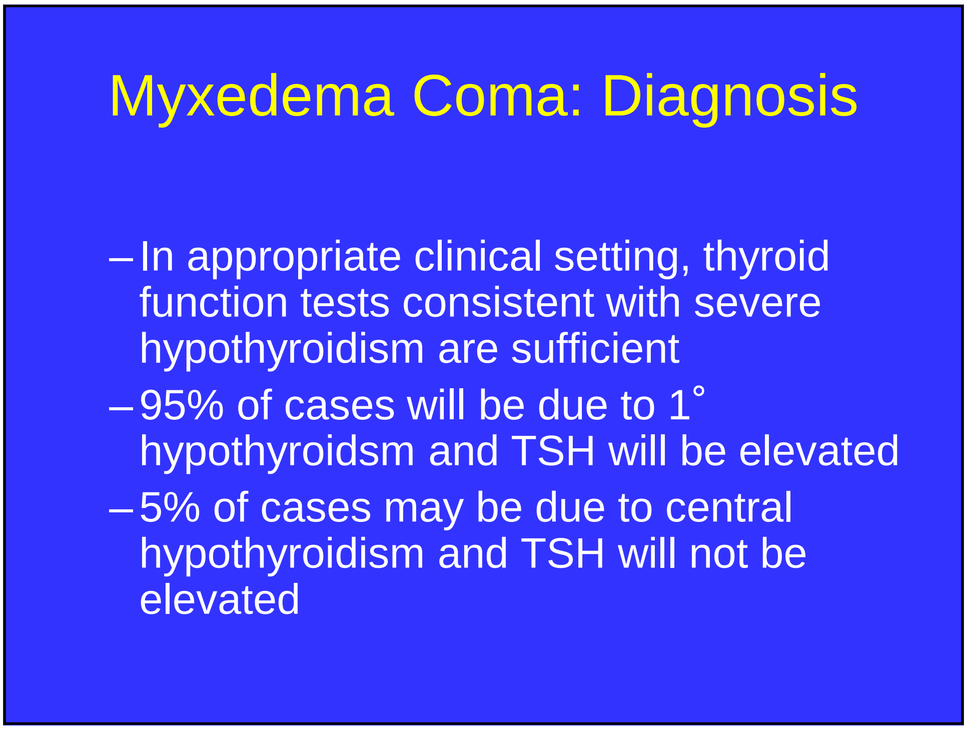
Eur J Endocrinol2006;154(4):533.

Myxedema Coma

- Definition: neurologic depression due to severe thyroid hormone deficiency (actual coma is not necessary)
- Mortality: Mortality rate reported at 30%-50%
- Precipitating factors
  - Medication non-compliance
  - Cold weather
  - Infection
  - MI/CVA
  - CNS depressant medications: narcotics, anesthetics, sedatives

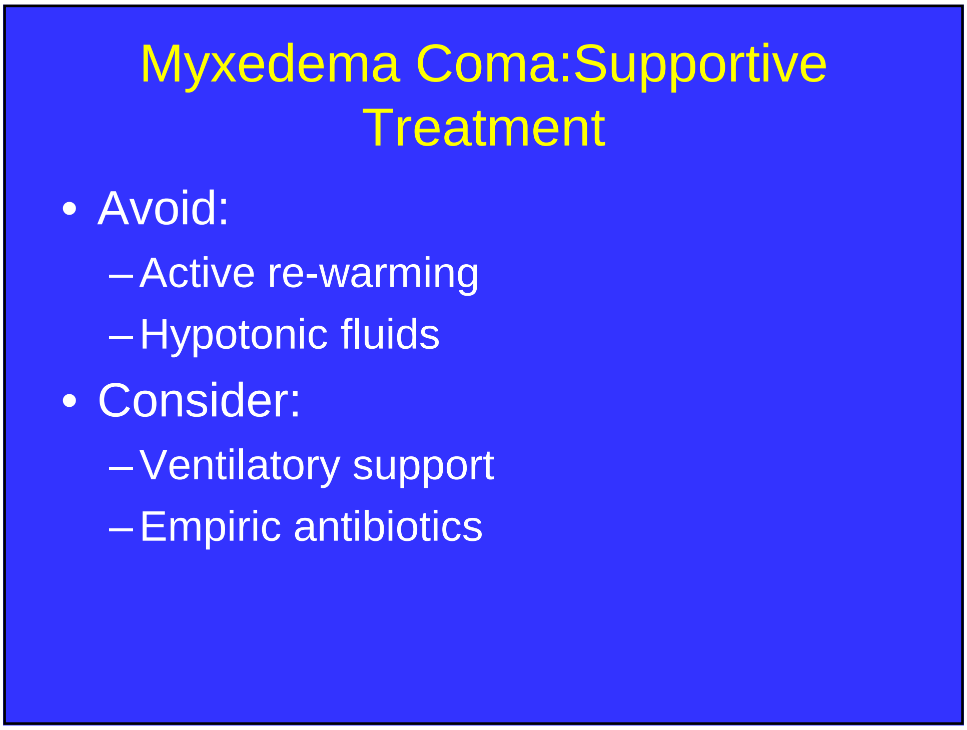
Myxedema Coma

- Clinical features
  - Lethargy, obtundation, coma, seizures
  - Bradycardia
  - Hypotension
  - Hypothermia
  - Hypoventilation with CO2 retention
  - Hyponatremia due to failure to suppress ADH
  - Ileus



Myxedema Coma: Diagnosis

- In appropriate clinical setting, thyroid function tests consistent with severe hypothyroidism are sufficient
- 95% of cases will be due to 1° hypothyroidsm and TSH will be elevated
- 5% of cases may be due to central hypothyroidism and TSH will not be elevated



Myxedema Coma:Supportive Treatment

- Avoid:
  - Active re-warming
  - Hypotonic fluids
- Consider:
  - Ventilatory support
  - Empiric antibiotics

Myxedema Coma: Treatment

- Administer:
  - Glucocorticoids
    - Prudent to administer hydrocortisone 50-100 mg tid for several days
    - 1° or 2° adrenal insufficiency may coexist: screen prior to Rx if possible

Myxedema Coma: Treatment

Administer:

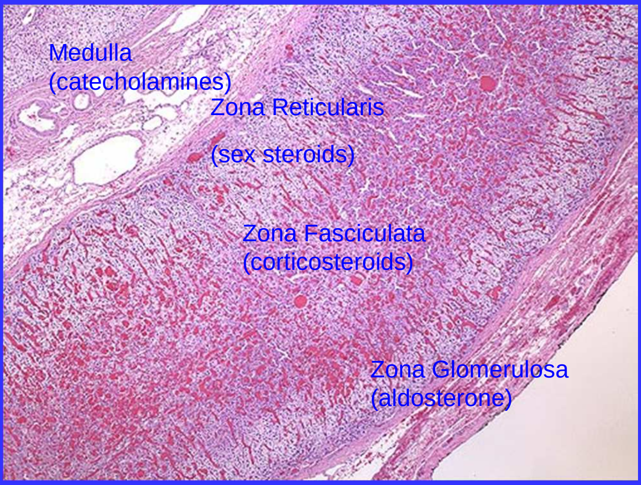
- Thyroid hormone
  - 300-500 µg T4 given iv followed by 100 µg iv qd
  - **OR** Combination of T4(at 50% of dose) and T3 10µg iv q 8 hours
  - When patient alert and taking po switch to oral replacement
  - Improvement in mentation, temperature, pulse and Na occur quickly
  - TSH response will be gradual

J Endocrinol. 2004;180(2):347

Myxedema Coma: Treatment

- Special Consideration: CAD
  - CAD is common in patients with hypothyroidism
  - Untreated hypothyroidism may mask symptoms of CAD
  - If CAD is suspected, T4 replacement may be safer at dose of 200-250 µg iv as one time dose to reverse neurologic impairment followed by 25-50 µg T4 iv qd

Acute Adrenal Crisis

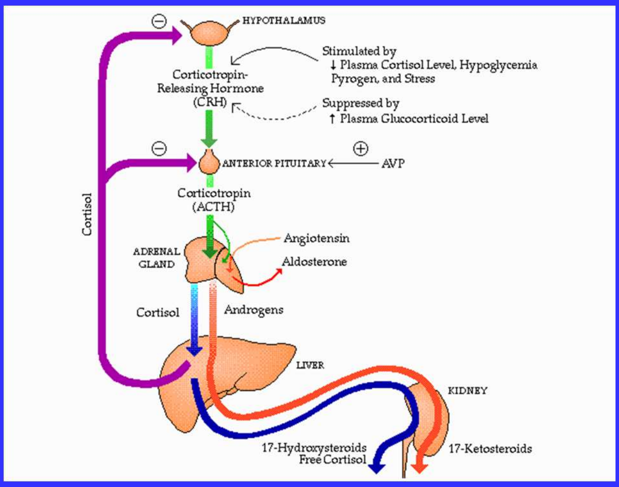

Medulla
(catecholamines)
Zona Reticularis
(sex steroids)
Zona Fasciculata
(corticosteroids)
Zona Glomerulosa
(aldosterone)

Slide courtesy of Graham McMahon, MD

Hypothalamic/Pituitary/Adrenal Axis

- ACTH stimulates secretion of cortisol
- ACTH can stimulate aldosterone
- RAS and K+ increase production of aldosterone
- In absence of ACTH cortisol IS NOT produced
- In absence of ACTH aldosterone IS secreted
- 1° adrenal insufficiency: adrenal failure
- 2° adrenal insufficiency: pituitary failure

Hypothalamic/Pituitary/Adrenal Axis


⊖
HYPOTHALAMUS
Stimulated by
↓ Plasma Cortisol Level, Hypoglycemia
Pyrogen, and Stress
Corticotropin-Releasing Hormone (CRH)
Suppressed by
↑ Plasma Glucocorticoid Level
⊖
⊕
ANTERIOR PITUITARY
AVP
Corticotropin (ACTH)
Cortisol
ADRENAL GLAND
Angiotensin
Aldosterone
Cortisol
Androgens
LIVER
KIDNEY
17-Hydroxysteroids
Free Cortisol
17-Ketosteroids

Acute Adrenal Crisis

- Effects of cortisol
  - Maintain blood pressure by sensitizing vascular smooth muscle to catecholamine pressor effects
  - Antagonize effect of ADH on free water excretion and suppress ADH secretion
  - Increase hepatic gluconeogenesis

Acute Adrenal Crisis

- Effects of aldosterone include
  - Na retention
  - Potassium excretion
  - Maintain extracellular volume
  - Increase vascular resistance

Acute Adrenal Crisis:Signs

- Nausea, abdominal pain
- Fatigue, weight loss
- Hypotension
- Fever
- Hyponatremia
- Eosinophilia
- Hypoglycemia

Acute Adrenal Crisis:1° vs 2 °

- 1°
  - Hyperkalemia
  - Hyperpigmentation due to elevated ACTH
  - Dehydration and hypotension
- 2 °
  - Less hypotension
  - More hypoglycemia
  - Loss of other pituitary hormones

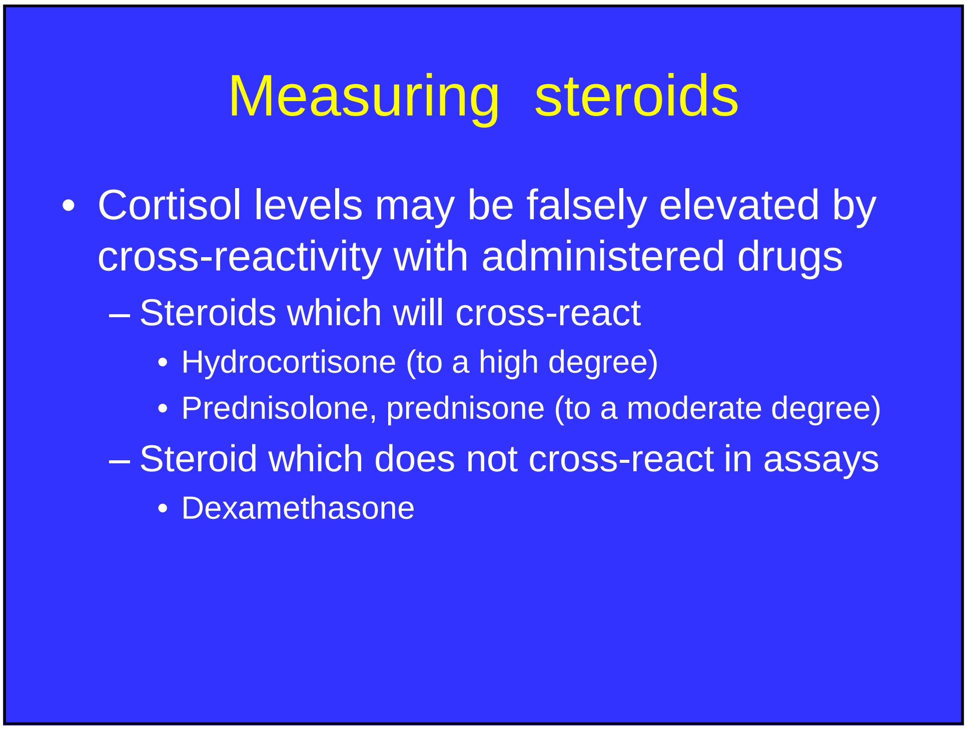
Precipitants of acute adrenal crisis

- Acute ***stress*** in patient with undiagnosed chronic adrenal insufficiency
- Abrupt ***cessation of glucocorticoids*** in adrenally insufficient patient or failure to increase dose in setting of stress
- Bilateral adrenal ***hemorrhage***
- Pituitary ***infarction***
- Medications inhibiting cortisol production:
    - Etomidate, ketoconazole, megestrol

Adrenal Testing: ACTH stim test

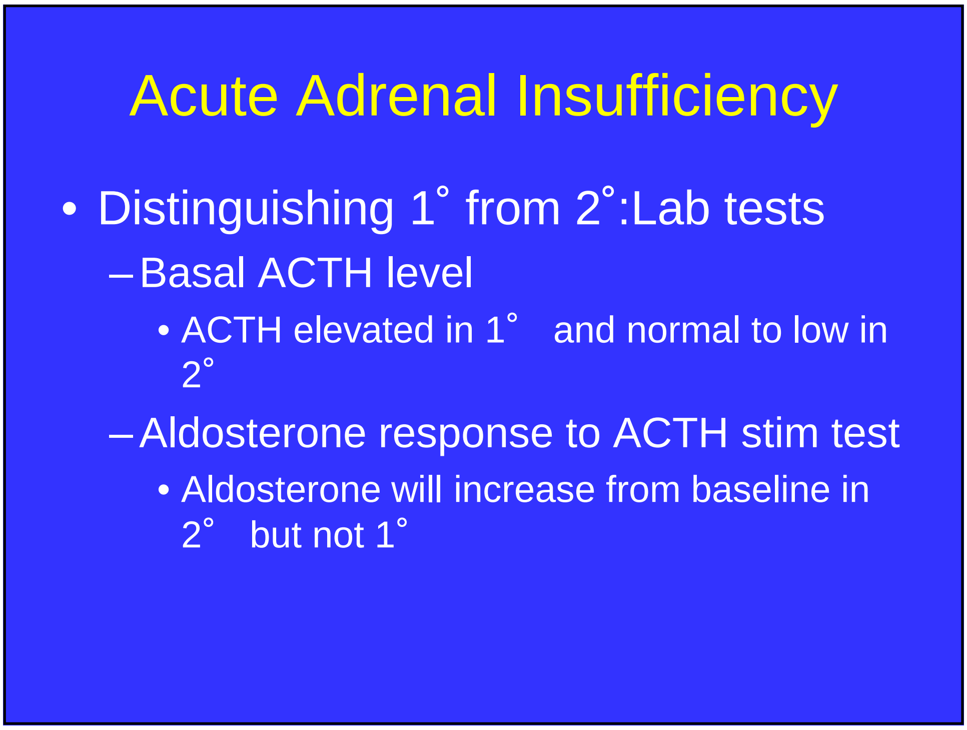
Standard test 250 μg iv or im
Low dose test 1 μg iv(may be helpful in recent onset 2º)

• Random/AM cortisol (μg/dl)	AM
– Makes adrenal insufficiency likely	<3μg/dl
– Makes adrenal insufficency unlikely	>11μg/dl
• After ACTH stimulation (30,60 min)	
– Makes adrenal insufficiency likely	<18μg/dl
– Makes adrenal insufficency unlikely	>20μg/dl



Measuring steroids

- Cortisol levels may be falsely elevated by cross-reactivity with administered drugs
  - Steroids which will cross-react
    - Hydrocortisone (to a high degree)
    - Prednisolone, prednisone (to a moderate degree)
  - Steroid which does not cross-react in assays
    - Dexamethasone



Acute Adrenal Insufficiency

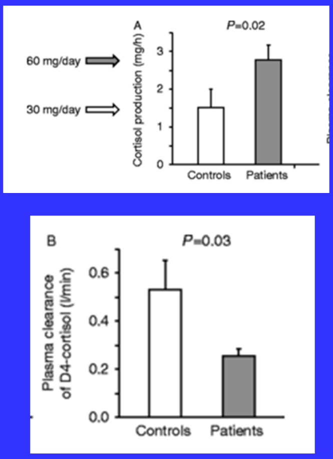
- Distinguishing 1° from 2°:Lab tests
  - Basal ACTH level
    - ACTH elevated in 1° and normal to low in 2°
  - Aldosterone response to ACTH stim test
    - Aldosterone will increase from baseline in 2° but not 1°

Acute Adrenal Insufficiency: Treatment

- Infuse normal saline or D5NS 1-3 liters over 12-24 hours
- 50 mg iv hydrocortisone q 6 hours X 24 hours followed by 50mg iv q 8 hours and tapered to physiologic replacement if needed
- Dexamethasone
  - Will not supply mineralocorticoid replacement in 1° adrenal insufficiency
- Saline will be adequate to replace mineralocorticoid needs acutely until diagnosis established
- Average maintenance dose
  - Hydrocortisone 15-20 mg qam and 5-10 mg qpm
  - Fludrocortisone .1 mg qd

Critical Illness Related Corticosteroid Insufficiency (CIRCI)

- In critical illness cortisol binding globulin may be *decreased* lowering total measured cortisol but *not* free cortisol
- Degradation of cortisol is decreased prolonging half-life and even 200 mg/day may be more than necessary



Eur J Endocrinol July 1, 2016 vol. 175 no. 1 R1-R9

CIRCI: What to do

- Possibility of “relative” adrenal insufficiency raised in septic patients with refractory hypotension
- Treatment with high(200 mg/day)steroids has been inconsistently found to improve mortality
- Generally ACTH stim testing is not recommended with normal baseline cortisol
- Treatment with glucocorticoids should be reserved for selected patients

ClinEndocrinol(Oxf)2015 ;83(3):289-97

Case

- 22 yr old ♀ with hypothyroidism and celiac disease presents to ER with “worst headache of my life”
- Patient has missed “a few” doses of thyroid hormone, but restarted
- Denies any other symptoms
- CT scan shows no lesions
- LP showed pressure above manometer readings

Case

- Labs remarkable for:
  - TSH 151 (nl to 5) T4 2.4 (nl 4.6-11) T3 64 (nl 80-200)
  - Glucose 52
  - Na 131 K 4.3
- Patient had acute deterioration in mental status
- She was treated with mannitol, and dexamthasone X1 and transferred to ICU

Case

- After transfer she received 63 mcg iv T4
- 30 hours after transfer she became hypotensive requiring pressors
- What happened?

Case

- Labs sent at time of hypotension showed:
  - Cortisol .6 µg/dl
  - Aldosterone undetectable
  - ACTH 1100 (nl up to 30)
  - Antibodies to 21-hydoxylase enzyme c/w Addison's disease

Case

- Patient had known hypothyroidism not adequately treated because of non-compliance as well as undiagnosed adrenal insufficiency
- Patient developed pseudotumor cerebri
- Dexamethasone "covered" glucocorticoid needs for short time
- Stress and replacement of thyroid hormone led to acute adrenal crisis

Hypercalcemic Crisis

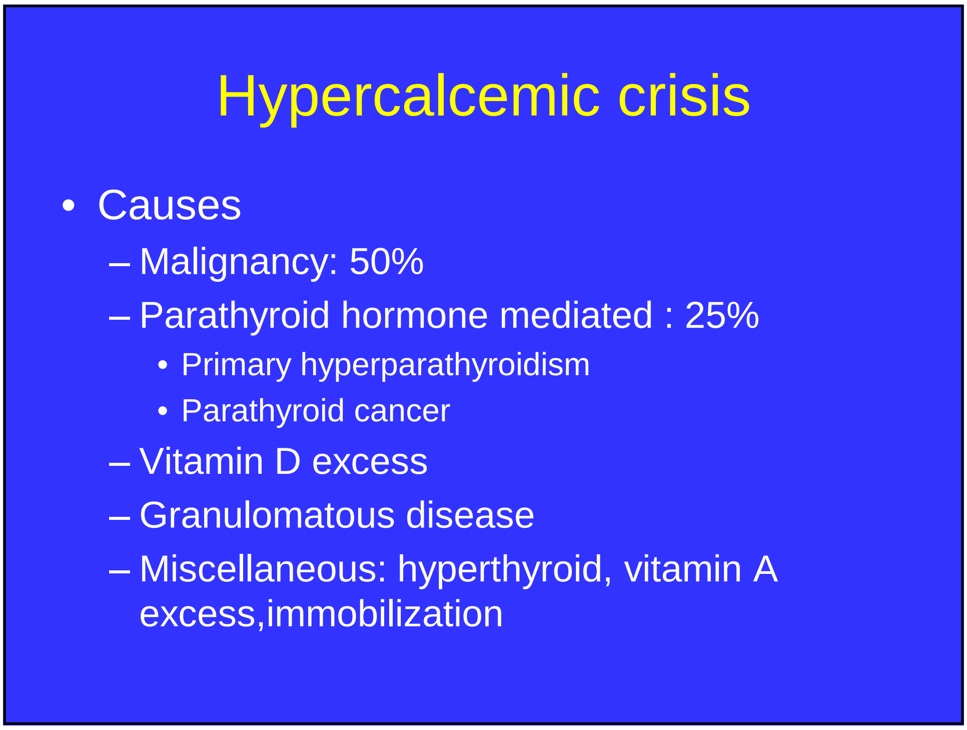
- Definition
  - Corrected* serum calcium over 14 mg/dl
  - Evidence of organ dysfunction
- Symptoms
  - Polyuria, dehydration due to concentrating defect
  - Nausea, vomiting, abdominal pain
  - Confusion, somnolence, coma

*Correction for low albumin is increase of .8mg/dl calcium for each 1 mg/dl below 4 mg/dl of albumin

Hypercalcemic crisis

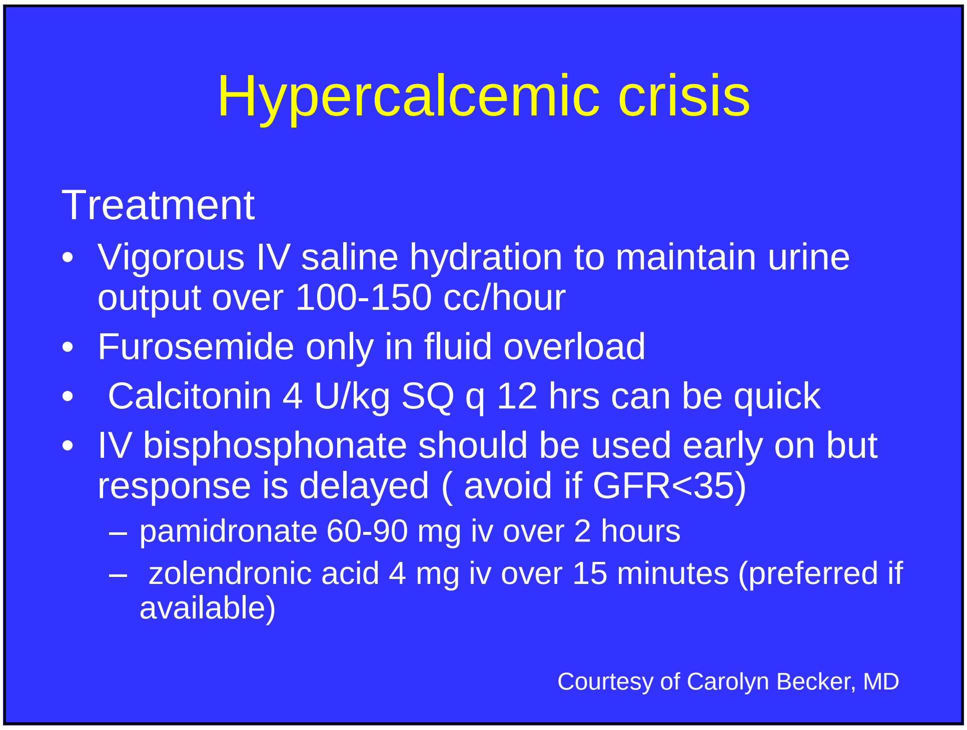
Laboratory and radiologic abnormalities

- Renal impairment
- Pancreatitis
- Ectopic calcifications including nephrocalcinosis
- EKG changes including shortened QTc interval, heart block, and ventricular arrythmias



Hypercalcemic crisis

- Causes
  - – Malignancy: 50%
  - – Parathyroid hormone mediated : 25%
    - Primary hyperparathyroidism
    - Parathyroid cancer
  - – Vitamin D excess
  - – Granulomatous disease
  - – Miscellaneous: hyperthyroid, vitamin A excess,immobilization



Hypercalcemic crisis

Treatment

- Vigorous IV saline hydration to maintain urine output over 100-150 cc/hour
- Furosemide only in fluid overload
- Calcitonin 4 U/kg SQ q 12 hrs can be quick
- IV bisphosphonate should be used early on but response is delayed (avoid if GFR<35)
  - – pamidronate 60-90 mg iv over 2 hours
  - – zolendronic acid 4 mg iv over 15 minutes (preferred if available)

Courtesy of Carolyn Becker, MD

Hypercalcemic crisis

Treatment alternatives if hypercalcemia persists

- Cinacalcet 30 mg PO 1-2 x per day for 1° HPT as bridge to surgery
- Glucocorticoids (prednisone 40 mg qd)if vitamin D toxicity, granulomatous disease or myeloma is suspected
- Denosamab 120 mg sc if malignancy is suspected
- Dialysis for severe renal failure

Summary

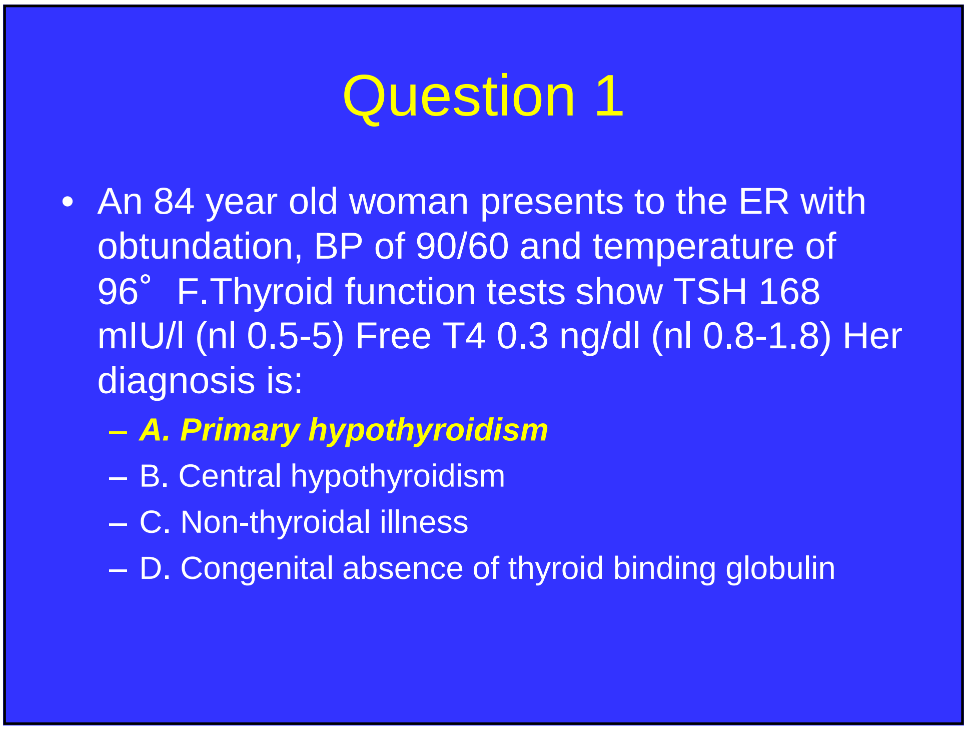
- Thyroid Storm
  - Diagnosis requires clinical suspicion in appropriate setting
  - Prompt treatment includes anti-thyroid medication, iodine,dexamethasone and beta-blockers
- Myxedema Coma
  - Diagnosis requires clinical suspicion in appropriate setting
  - Treatment includes iv steroid replacement and iv thyroid hormone

Summary

- Adrenal insufficiency
  - Diagnosis can be confirmed by ACTH stimulation testing
  - Treatment includes glucocorticoid replacement; mineralocorticoid replacement if primary adrenal insufficiency present
- Hypercalcemia
  - Fluid replacement with saline initial therapy
  - Iv bisphosphonate therapy if adequate renal function
  - Identify etiology

Question 1

- An 84 year old woman presents to the ER with obtundation, BP of 90/60, temperature of 96° F.Thyroid function tests show TSH 168 mIU/l (nl 0.5-5) Free T4 0.3 ng/dl (nl 0.8-1.8) Her diagnosis is:
  - A. Primary hypothyroidism
  - B. Central hypothyroidism
  - C. Non-thyroidal illness
  - D. Congenital absence of thyroid binding globulin



Question 1

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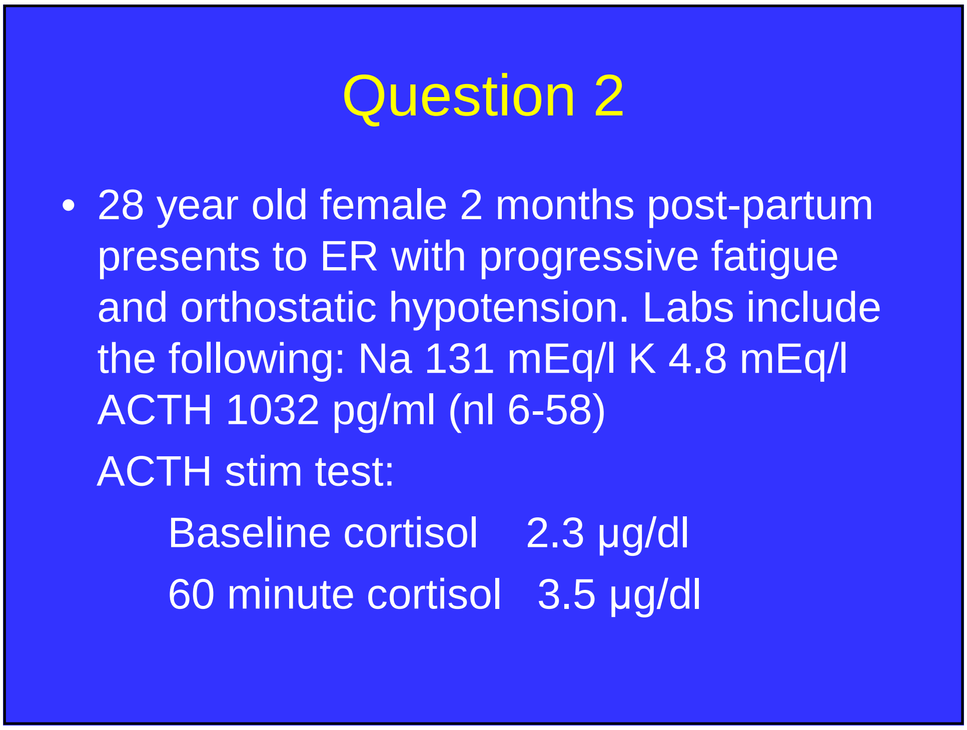
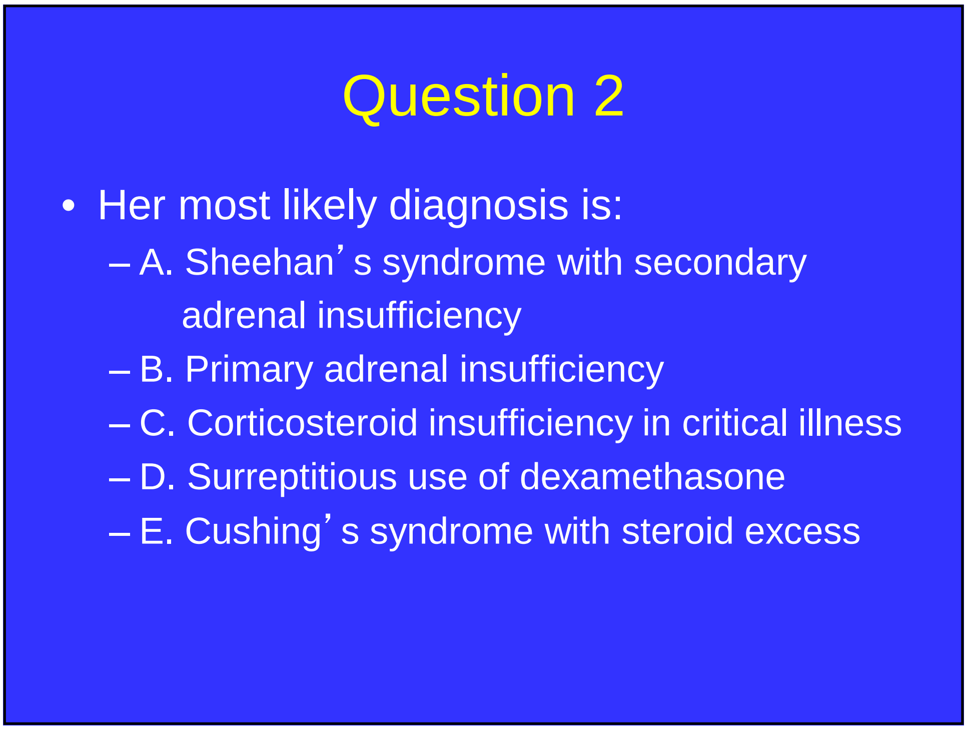


Question 2

- 28 year old female 2 months post-partum presents to ER with progressive fatigue and orthostatic hypotension. Labs include the following: Na 131 mEq/l K 4.8 mEq/l ACTH 1032 pg/ml (nl 6-58)

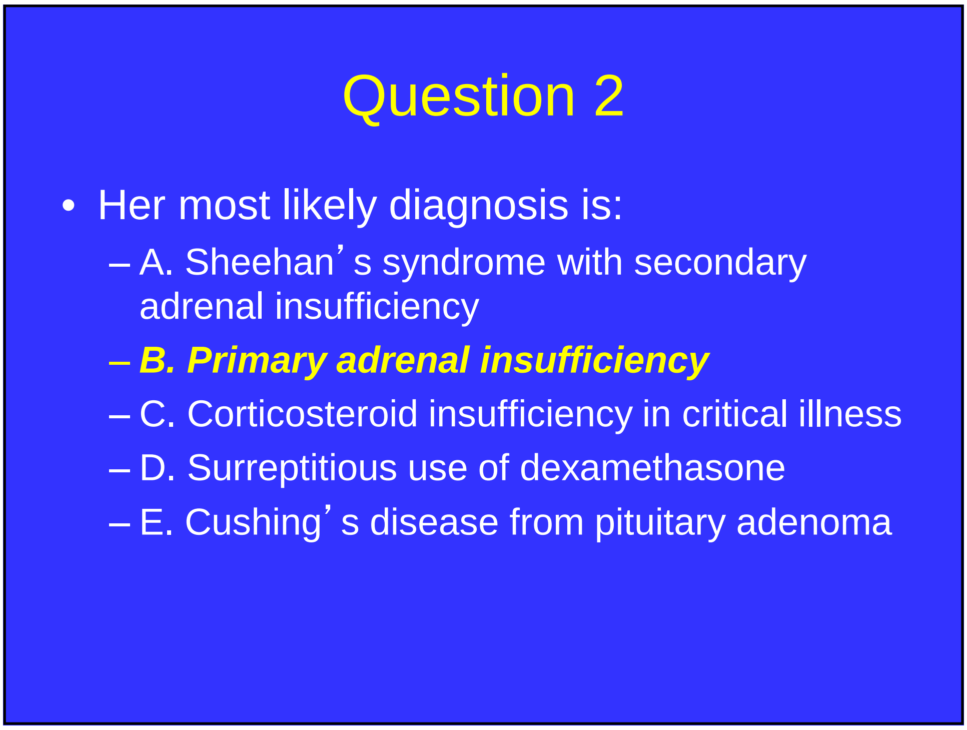
ACTH stim test:

Baseline cortisol 2.3 µg/dl
60 minute cortisol 3.5 µg/dl



Question 2

- Her most likely diagnosis is:
  - A. Sheehan's syndrome with secondary adrenal insufficiency
  - B. Primary adrenal insufficiency
  - C. Corticosteroid insufficiency in critical illness
  - D. Surreptitious use of dexamethasone
  - E. Cushing's syndrome with steroid excess



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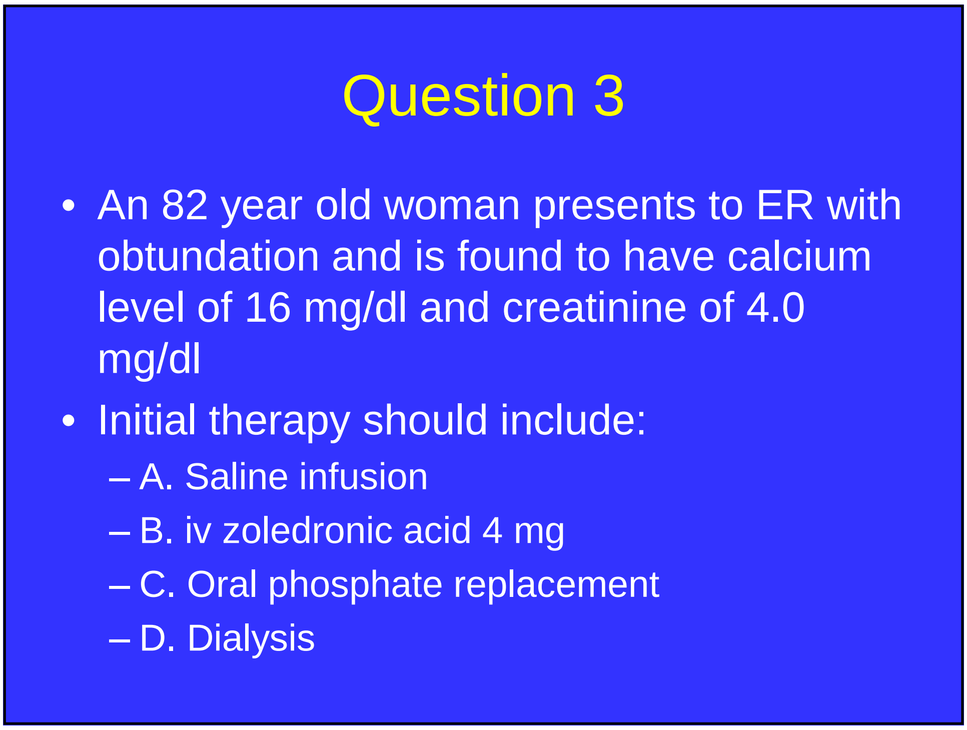
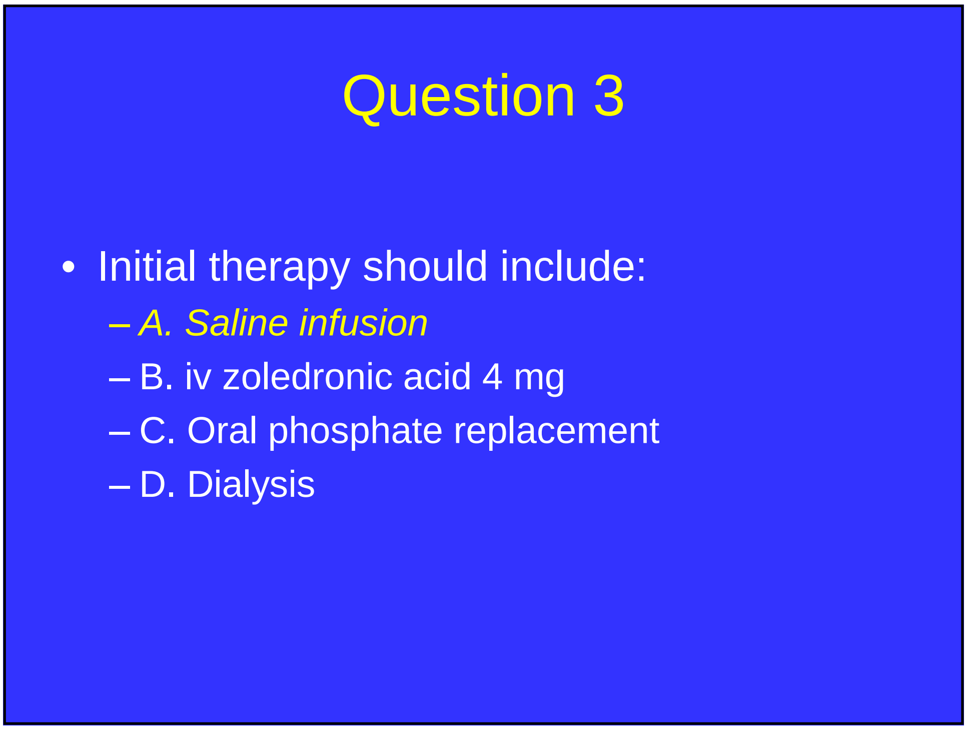
- Her most likely diagnosis is:
  - A. Sheehan's syndrome with secondary adrenal insufficiency
  - ***B. Primary adrenal insufficiency***
  - C. Corticosteroid insufficiency in critical illness
  - D. Surreptitious use of dexamethasone
  - E. Cushing's disease from pituitary adenoma



Question 3

- An 82 year old woman presents to ER with obtundation and is found to have calcium level of 16 mg/dl and creatinine of 4.0 mg/dl
- Initial therapy should include:
  - A. Saline infusion
  - B. iv zoledronic acid 4 mg
  - C. Oral phosphate replacement
  - D. Dialysis



Question 3

- Initial therapy should include:
  - *A. Saline infusion*
  - B. iv zoledronic acid 4 mg
  - C. Oral phosphate replacement
  - D. Dialysis

Financial Disclosures

- None

Selected References

- Thyrotoxicosis and Thyroid Storm B. Nayak and K Burman Endocrinology and Metabolism Clinics of North America 35:663-686, 2006
- Myxedema Coma L. Wartofsky Endocrinology and Metabolism Clinics of North America 35:687-698, 2006
- Hypercalcemic Crisis: A Clinical Review Ahmad et al American Journal of Medicine 128:239-245, 2015

End of Lecture

Board Question

- Treatment of thyroid storm includes all but which of the following?
  - A. Iodine
  - B. Dexamethsaone
  - C. Thionamide
  - D. Aspirin
  - E. Beta-blocker

Board Question

- Treatment of thyroid storm includes all but which of the following?
  - A. Iodine
  - B. Dexamethsaone
  - C. Thionamide
  - *D. Aspirin*
  - E. Beta-blocker

Board Question

- Initial treatment for Thyroid storm should be PTU if possible: rectal administration may be needed for ileus
- Iodine, usually as SSKI, is administered shortly afterward
- Dexamthasone and beta-blockers and administered next
- Aspirin should not be administered for hyperpyrexia because of displacement of thyroid hormones from binding proteins

26883074

Post-test Question

- Post-test question for Endocrine Crises in the ICU
- A 60 year old woman with a history of a recent 40 lb weight loss presents to the emergency room with agitation and confusion. She has an ileostomy(from remote history of ruptured appendix and complications) with significant increase in output for past 4 days.
- On physical exam BP is 100/60. Pulse 130 and consistent with afib, skin is unremarkable and neck shows possible thyroid nodule. Neurologic exam is non-focal with patient oriented X 1 only.
- Initial labs are remarkable for:
- BUN 47 mg/dl and creatinine 1.68(baseline .9)mg/dl
- Glucose 130 mg/dl
- Calcium 11.2 mg/dl Phos 4.5mg/dl
- Cortisol 14 microgram/dl
- TSH .01 microIU/ml (nl .5-5)
- Free T4 5.9 ng/dl(nl .8-1.9)

- Albumin 3.2 mg/dl
- Most likely diagnosis is:
- A. Hypercalcemic crisis
- B. Adrenal insufficiency
- C. Central hypothyroidism
- D. Thyroid storm
- Answer: D
- Explanation
- This level of calcium elevation in a patient with near normal albumin is unlikely to account for abnormal mental status though it could contribute to her dehydration. Adrenal insufficiency could lead to mild hypercalcemia, hypotension and weight loss but baseline cortisol level is high enough to suggest looking for other explanations. Central hypothryoidsim will not present with elevated free T4 levels. *Hyperthyroidism could lead to weight loss, atrial fibrillation, mild hypercalcemia and dehydration. Thyroid function tests are consistent with that. Burch-Wartofsky score would be 10 points for neurologic changes, 10 points for diarrhea, 20 points for tachycardia and an additional 10 points for new atrial fibrillation. This high score(50) raises concern for thyroid storm and she should initially be treated as such.*

Question 4

- Laboratory findings found in thyroid storm may include all but which of the following?
  - A. elevated TSH
  - B. elevated LFTs
  - C. elevated calcium
  - D. elevated glucose
  - E. elevated BUN

Question 4

- Laboratory findings found in thyroid storm may include all but which of the following?
  - ***A. elevated TSH***
  - B. elevated LFTs
  - C. elevated calcium
  - D. elevated glucose
  - E. elevated BUN

Question 5

- 60 year old woman with a history of a recent 40 lb weight loss presents to the emergency room with agitation and confusion. She has an ileostomy(from remote history of ruptured appendix and complications) with significant increase in output for past 4 days.

Question 5

- On physical exam BP is 100/60. Pulse 130 and consistent with afib, skin is unremarkable and neck shows possible thyroid nodule. Neurologic exam is non-focal with patient oriented X 1 only.

Question 5

- Labs remarkable for:
- BUN 47 mg/dl and creatinine 1.68(baseline .9)mg/dl
- Glucose 130 mg/dl
- Calcium 11.2 mg/dl Phos 4.5mg/dl
- Cortisol 14 microgram/dl
- TSH .01 microIU/ml (nl .5-5) Free T4 5.9 ng/dl(nl .8-1.9)
- Albumin 3.2 mg/dl

Question 5

- Most likely diagnosis is:
- A. Hypercalcemic crisis
- B. Adrenal insufficiency
- C. Central hypothyroidism
- D. Thyroid storm

Question 5

- Answer:
- A. This level of calcium elevation in a patient with near normal albumin is unlkely to account for abnormal mental status though it could contribute to her dehydration
- B. Adrenal insufficiency could lead to mild hypercalcemia, hypotension and weight loss but cortisol level is too high
- C. Central hypothryoidsim will not present with elevated free T4 levels
- D. *Hyperthyroidism could lead to weight loss, atrial fibrillation, mild hypercalcemia and dehydration and thyroid function tests are consistent with that. Neurologic changes as well as gastrointestional findings raise concern for thyroid storm and she should initially be treated as such*

Suboptimal Cortisol Production in Critical Illness

- Concept of relative adrenal insufficiency in critical illness has remained controversial
- No clear accepted definition exists
- Measurement of cortisol levels in the ICU may be impacted by low binding proteins and albumin
- ACTH stim test has not reliably identified patients in shock who will benefit from glucocorticoid therapy
- In cases of severe septic shock, glucocorticoids may be helpful but this is not established at this time by clinical trials

Fundamentals of Clinical Nutrition: Essentials for the Critical Care Specialist

Malcolm K. Robinson, MD
Associate Chair for Clinical Operations
Department of Surgery
Director, Nutrition Support Service
Brigham and Women's Hospital
Assistant Professor of Surgery
Harvard Medical School

I have no financial disclosures or conflicts of interest pertaining to this presentation

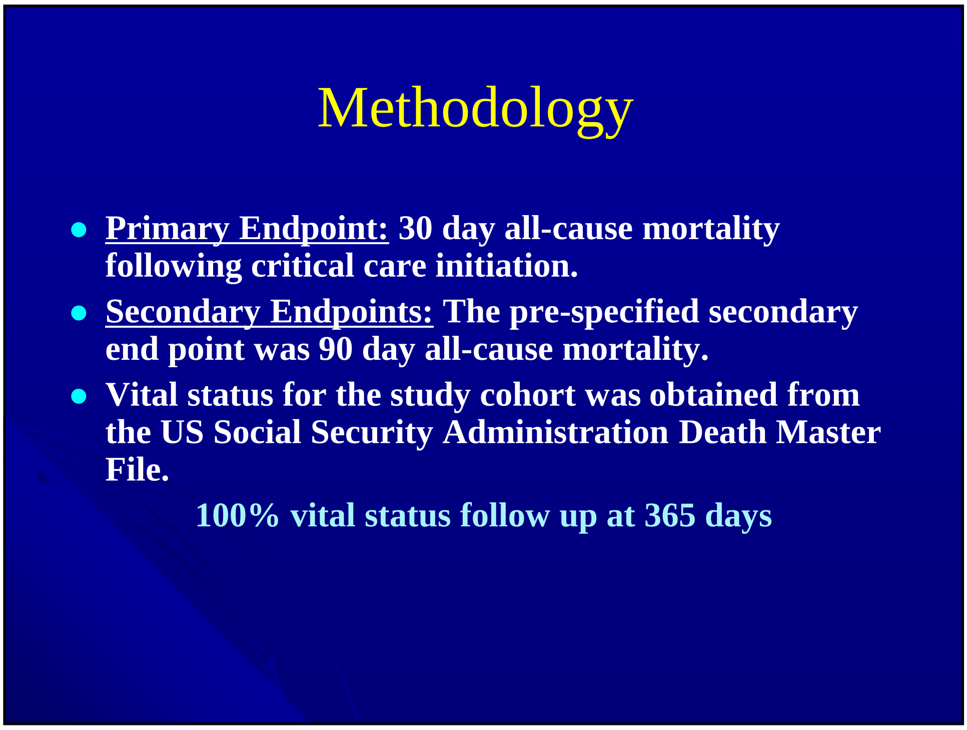
How does malnutrition affect outcome in the ICU?

Nutritional Status and Mortality in the Critically Ill*

Kris M. Mogensen, MS, RD, LDN, CNSC[1]; Malcolm K. Robinson, MD[2]; Jonathan D. Casey, MD[3];
Nicole S. Gunasekera, BA[4]; Takuhiro Moromizato, MD[5]; James D. Rawn, MD[2];
Kenneth B. Christopher, MD[6]

- Single-center, registry based observational cohort study.
- Nine medical and surgical ICUs in one hospital.
- 6,518 patients, age ≥ 18 years, who received a formal standardized evaluation by a registered dietitian between 2004 and 2011.

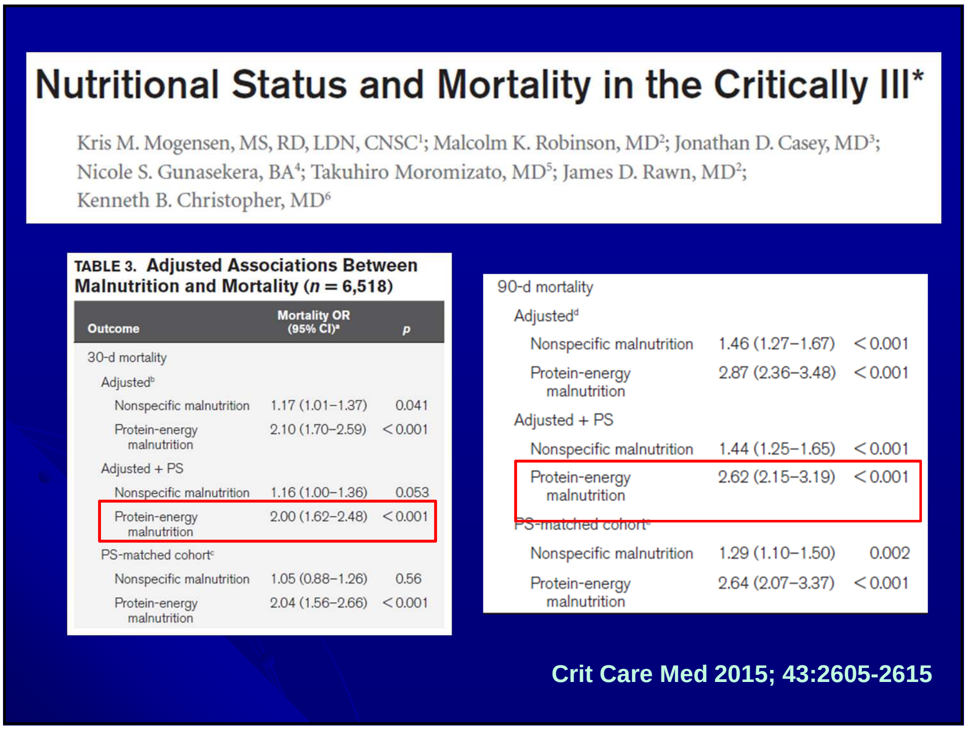
Crit Care Med 2015; 43:2605-2615



Methodology

- **Primary Endpoint:** 30 day all-cause mortality following critical care initiation.
- **Secondary Endpoints:** The pre-specified secondary end point was 90 day all-cause mortality.
- Vital status for the study cohort was obtained from the US Social Security Administration Death Master File.

100% vital status follow up at 365 days



Nutritional Status and Mortality in the Critically Ill*

Kris M. Mogensen, MS, RD, LDN, CNSC[1]; Malcolm K. Robinson, MD[2]; Jonathan D. Casey, MD[3]; Nicole S. Gunasekera, BA[4]; Takuhiro Moromizato, MD[5]; James D. Rawn, MD[2]; Kenneth B. Christopher, MD[6]

TABLE 3. Adjusted Associations Between Malnutrition and Mortality (*n* = 6,518)

Outcome	Mortality OR (95% CI)[a]	*p*
30-d mortality		
Adjusted[b]		
Nonspecific malnutrition	1.17 (1.01–1.37)	0.041
Protein-energy malnutrition	2.10 (1.70–2.59)	< 0.001
Adjusted + PS		
Nonspecific malnutrition	1.16 (1.00–1.36)	0.053
Protein-energy malnutrition	2.00 (1.62–2.48)	< 0.001
PS-matched cohort[c]		
Nonspecific malnutrition	1.05 (0.88–1.26)	0.56
Protein-energy malnutrition	2.04 (1.56–2.66)	< 0.001
90-d mortality		
Adjusted[d]		
Nonspecific malnutrition	1.46 (1.27–1.67)	< 0.001
Protein-energy malnutrition	2.87 (2.36–3.48)	< 0.001
Adjusted + PS		
Nonspecific malnutrition	1.44 (1.25–1.65)	< 0.001
Protein-energy malnutrition	2.62 (2.15–3.19)	< 0.001
PS-matched cohort[e]		
Nonspecific malnutrition	1.29 (1.10–1.50)	0.002
Protein-energy malnutrition	2.64 (2.07–3.37)	< 0.001

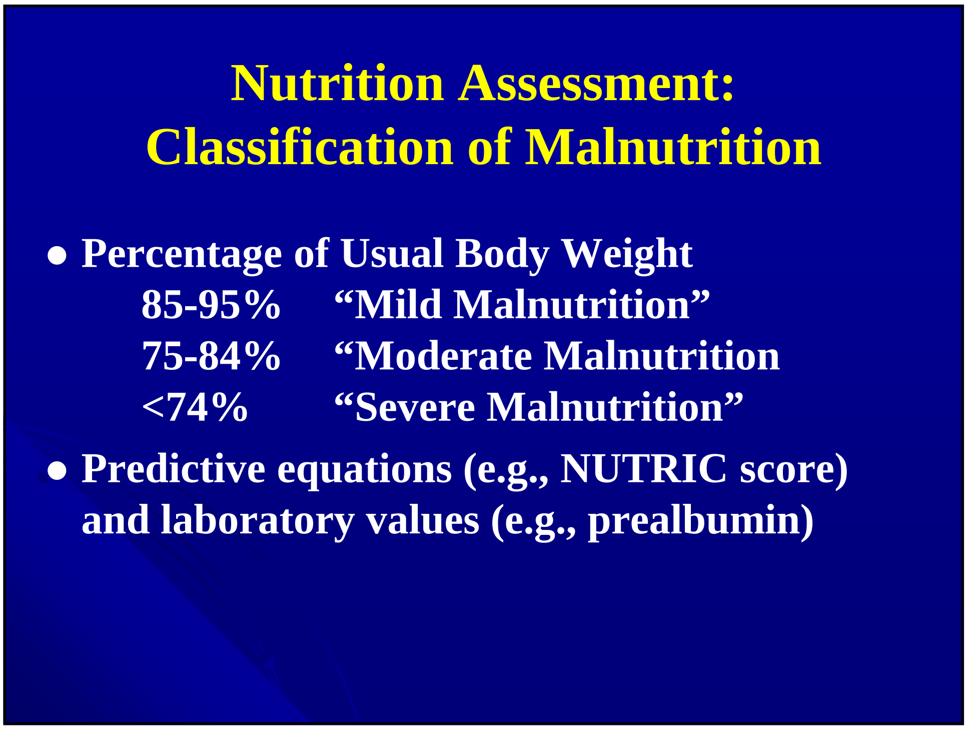
Crit Care Med 2015; 43:2605-2615

Fundamentals of Clinical Nutrition

- Nutrition Assessment
- Determining when and how to feed
- Tube feeding
- Basics of TPN

Nutrition Assessment

- **Obtain medical history, laboratory data and history of recent weight change.**
- **Determine nutritional status: well nourished versus mild, moderate or severe malnutrition.**
- **Calculate calorie and protein requirements.**
- **Make recommendation regarding nutritional intervention (if any).**

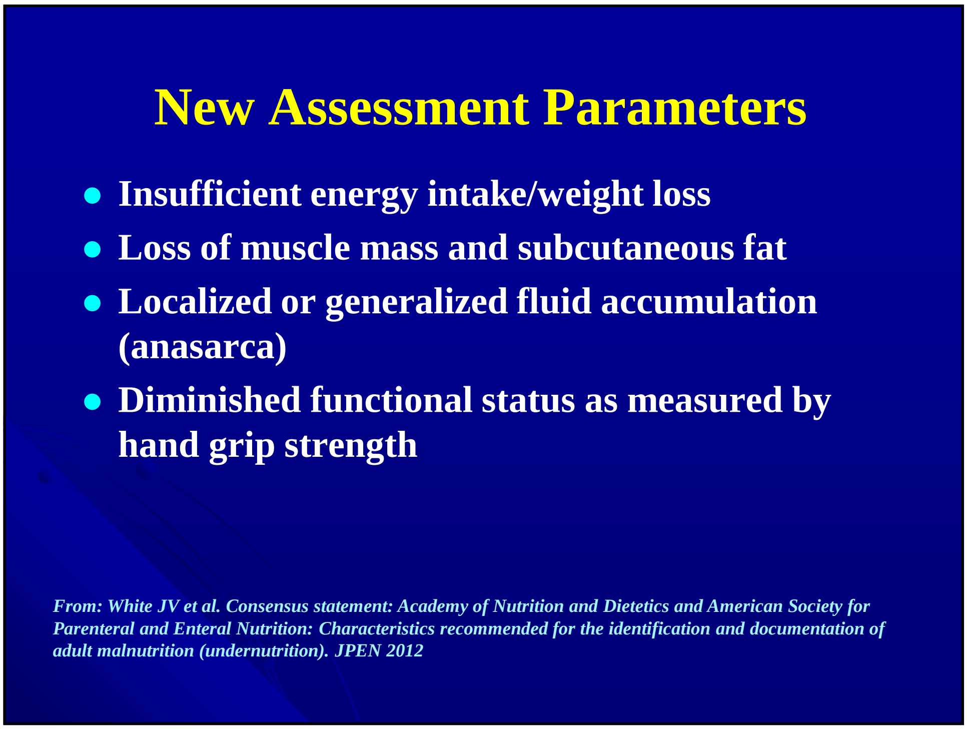


Nutrition Assessment: Classification of Malnutrition

- Percentage of Usual Body Weight

85-95%	“Mild Malnutrition”
75-84%	“Moderate Malnutrition
<74%	“Severe Malnutrition”

- Predictive equations (e.g., NUTRIC score) and laboratory values (e.g., prealbumin)

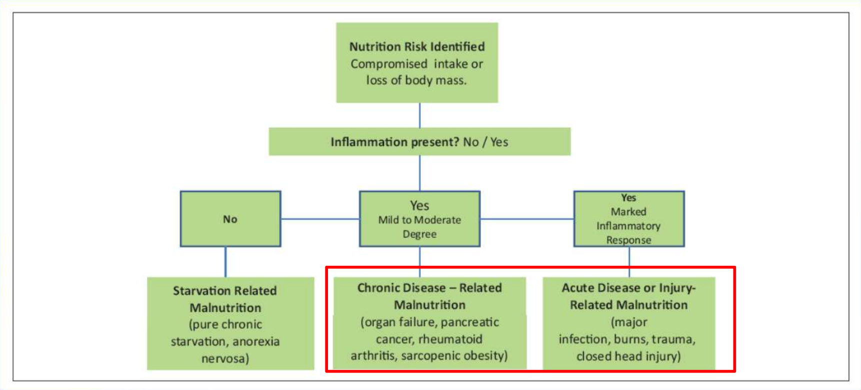


New Assessment Parameters

- Insufficient energy intake/weight loss
- Loss of muscle mass and subcutaneous fat
- Localized or generalized fluid accumulation (anasarca)
- Diminished functional status as measured by hand grip strength

From: White JV et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN 2012

Etiology-Based Malnutrition Diagnoses



Nutrition Risk Identified
Compromised intake or loss of body mass.

Inflammation present? No / Yes

No

Yes
Mild to Moderate Degree

Yes
Marked Inflammatory Response

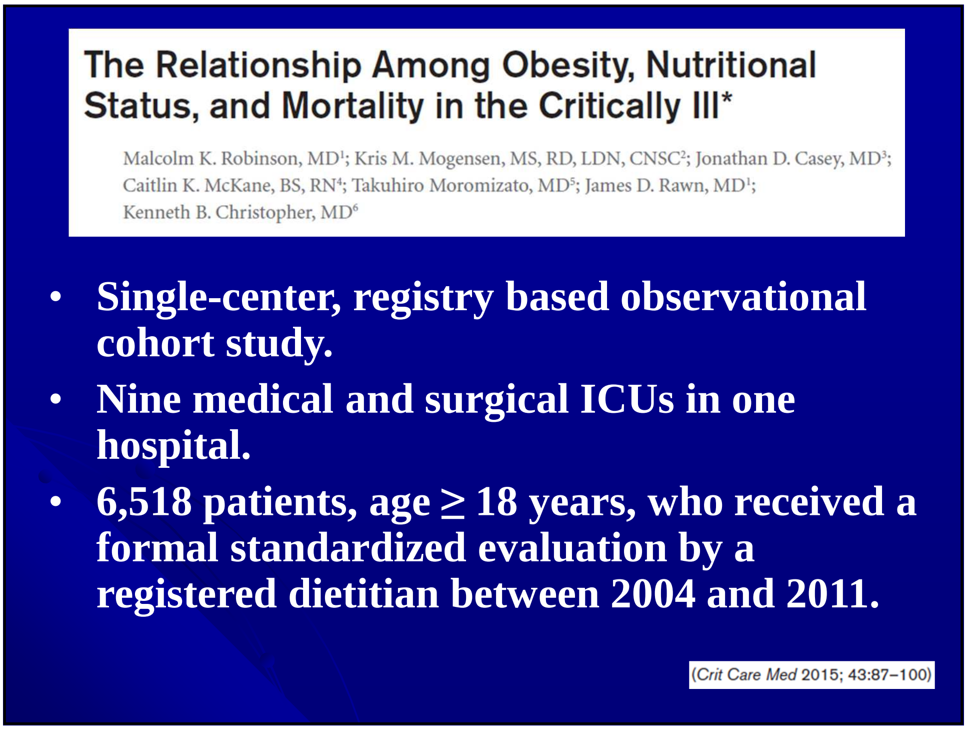
Starvation Related Malnutrition
(pure chronic starvation, anorexia nervosa)

Chronic Disease – Related Malnutrition
(organ failure, pancreatic cancer, rheumatoid arthritis, sarcopenic obesity)

Acute Disease or Injury-Related Malnutrition
(major infection, burns, trauma, closed head injury)

From: White JV et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN 2012

- Can obese patients be “malnourished?”
- Are obese people “protected” from bad outcomes in the ICU if they are malnourished?

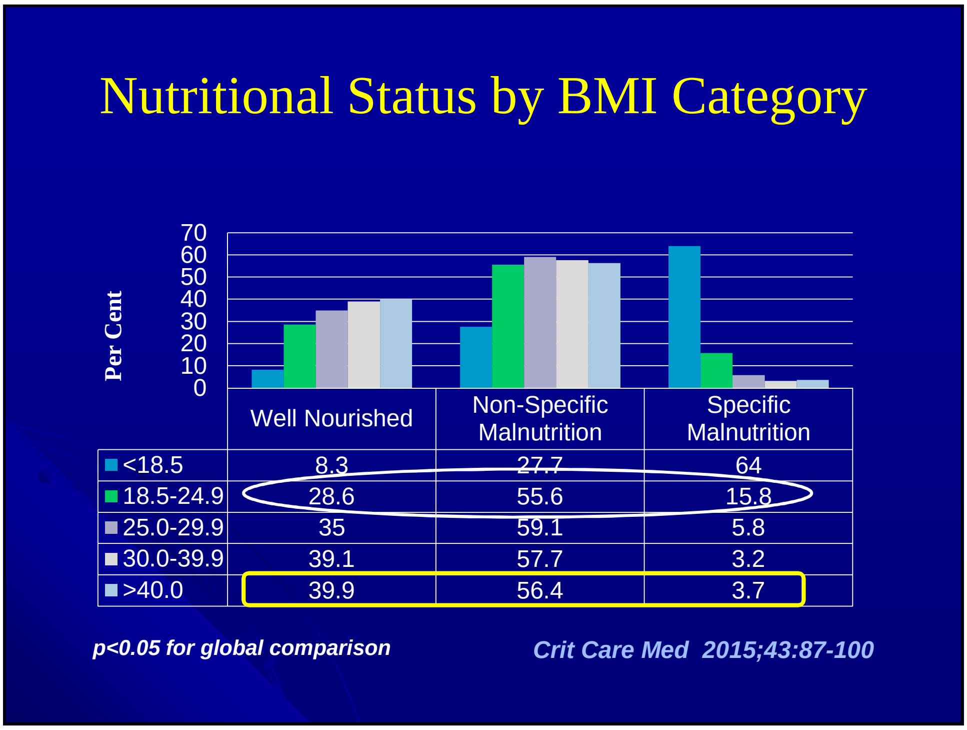


The Relationship Among Obesity, Nutritional Status, and Mortality in the Critically Ill*

Malcolm K. Robinson, MD[1]; Kris M. Mogensen, MS, RD, LDN, CNSC[2]; Jonathan D. Casey, MD[3]; Caitlin K. McKane, BS, RN[4]; Takuhiro Moromizato, MD[5]; James D. Rawn, MD[1]; Kenneth B. Christopher, MD[6]

- Single-center, registry based observational cohort study.
- Nine medical and surgical ICUs in one hospital.
- 6,518 patients, age ≥ 18 years, who received a formal standardized evaluation by a registered dietitian between 2004 and 2011.

(*Crit Care Med* 2015; 43:87–100)



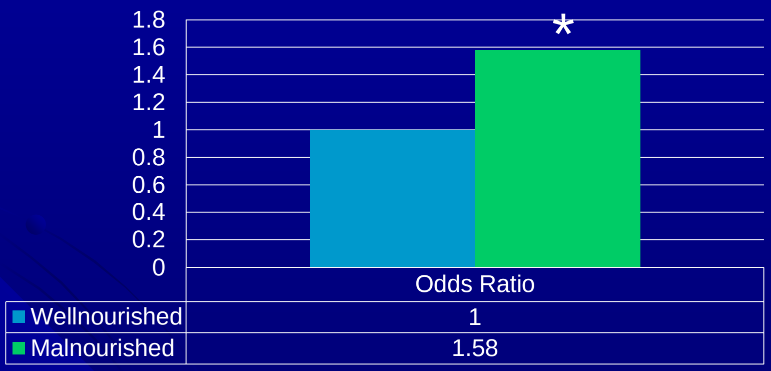
Nutritional Status by BMI Category

	Well Nourished	Non-Specific Malnutrition	Specific Malnutrition
■ <18.5	8.3	27.7	64
■ 18.5-24.9	28.6	55.6	15.8
■ 25.0-29.9	35	59.1	5.8
■ 30.0-39.9	39.1	57.7	3.2
■ >40.0	39.9	56.4	3.7

p<0.05 for global comparison

Crit Care Med 2015;43:87-100

Adjusted Odd Ratio for 30-day Mortality in Obese Critically Ill patients with and without Malnourishment



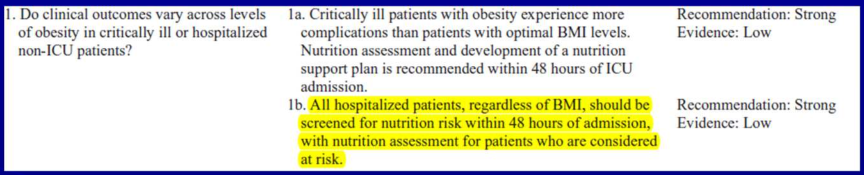
	Odds Ratio
■ Wellnourished	1
■ Malnourished	1.58

P =0.001 versus well nourished.

Crit Care Med 2015;43:87-100

- ➢Can obese patients be “malnourished?” YES
- ➢Are obese people “protected” from bad outcomes in the ICU if they are malnourished? NO

A.S.P.E.N. Clinical Guidelines: Nutrition Support of Hospitalized Adult Patients With Obesity



1. Do clinical outcomes vary across levels of obesity in critically ill or hospitalized non-ICU patients?	1a. Critically ill patients with obesity experience more complications than patients with optimal BMI levels. Nutrition assessment and development of a nutrition support plan is recommended within 48 hours of ICU admission.	Recommendation: Strong Evidence: Low
	1b. All hospitalized patients, regardless of BMI, should be screened for nutrition risk within 48 hours of admission, with nutrition assessment for patients who are considered at risk.	Recommendation: Strong Evidence: Low

(*JPEN J Parenter Enteral Nutr*. 2013;37:714-744)

Nutrition Assessment:
Estimating Energy Requirements

- There are many, many ways to estimate caloric needs.
- Predictive formulas exist for different patient populations e.g., ICU, obese, elderly, amputees, etc.
- Two of the most common ways to estimate caloric needs are:
  - Harris-Benedict equation
  - kcals/kg

Nutrition Assessment: Determining Daily Caloric Needs

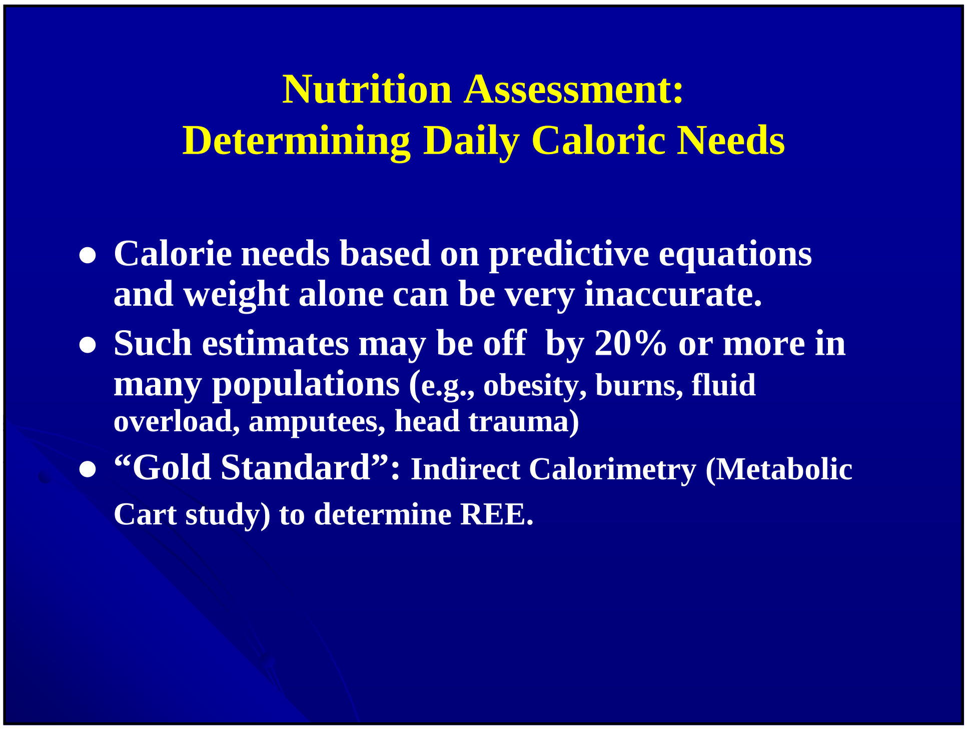
- Predictive formulas may be used to estimate BMR.
- Harris-Benedict Equations:

  Male BMR=66.47 + 13.75(W) + 5.0 (H) - 6.75 (A)

  Female BMR= 655.1 + 9.56 (W) + 1.85 (H) - 4.68 (A)
- Daily *Caloric* requirement based on BMR is: BMR x Activity (1.0-1.3) x Disease Stress (1.2-2.1)

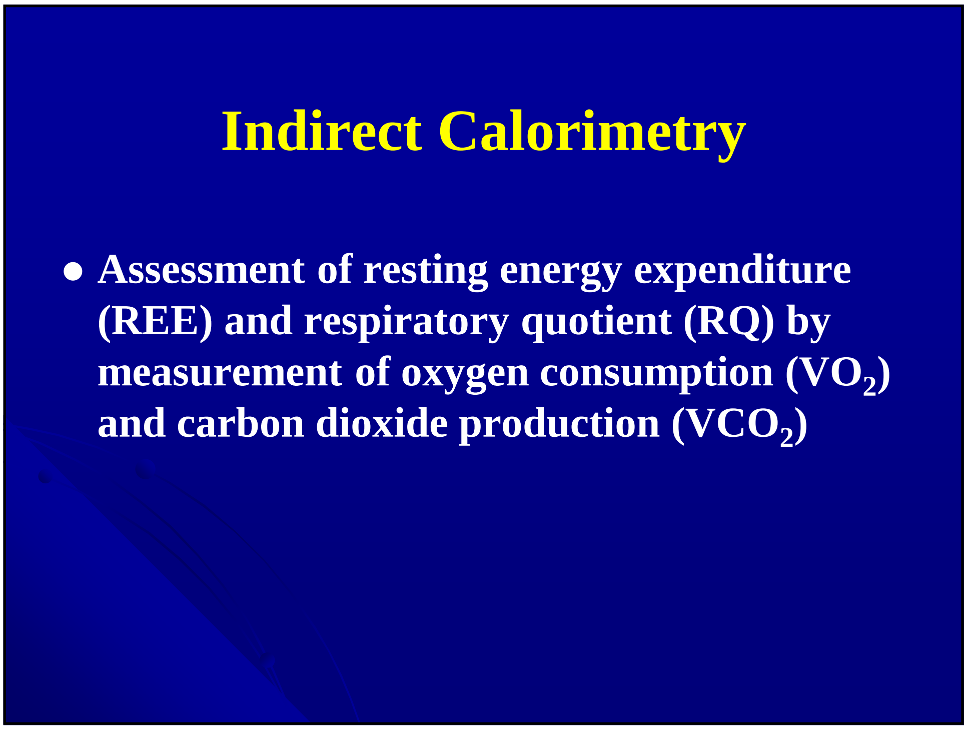
Nutrition Assessment: Determining Daily Caloric Needs

- Daily caloric needs may be estimated based on body weight alone.
- For seriously ill, hospitalized patients, caloric the goal may be estimated as 25-30 cals/kg.



Nutrition Assessment: Determining Daily Caloric Needs

- Calorie needs based on predictive equations and weight alone can be very inaccurate.
- Such estimates may be off by 20% or more in many populations (e.g., obesity, burns, fluid overload, amputees, head trauma)
- "Gold Standard": Indirect Calorimetry (Metabolic Cart study) to determine REE.



Indirect Calorimetry

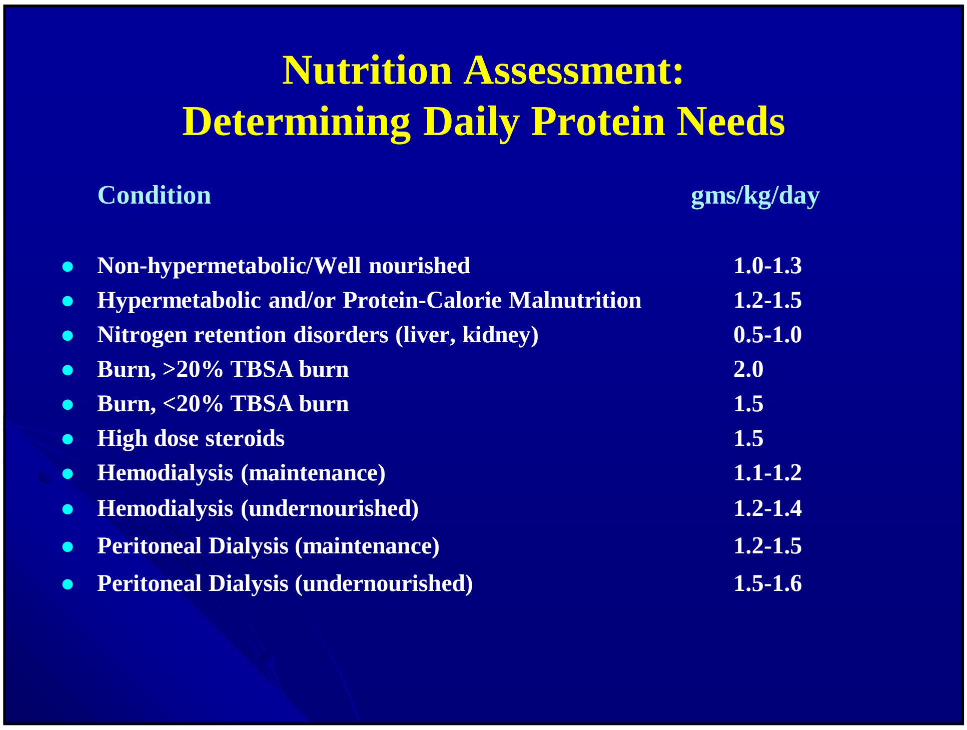
- Assessment of resting energy expenditure (REE) and respiratory quotient (RQ) by measurement of oxygen consumption (VO_2) and carbon dioxide production (VCO_2)

Weir Equation

- Complete:
  - REE (kcal/day)= [3.94 (VO_2)+1.1(VCO_2)] x 1.44 – 2.17(UN)
- Abbreviated:
  - REE (kcal/day)= [3.94 (VO_2)+1.1(VCO_2)] x 1.44
- Daily *Caloric* requirement based on REE is:
  - REE x activity factor (1.0-1.3)

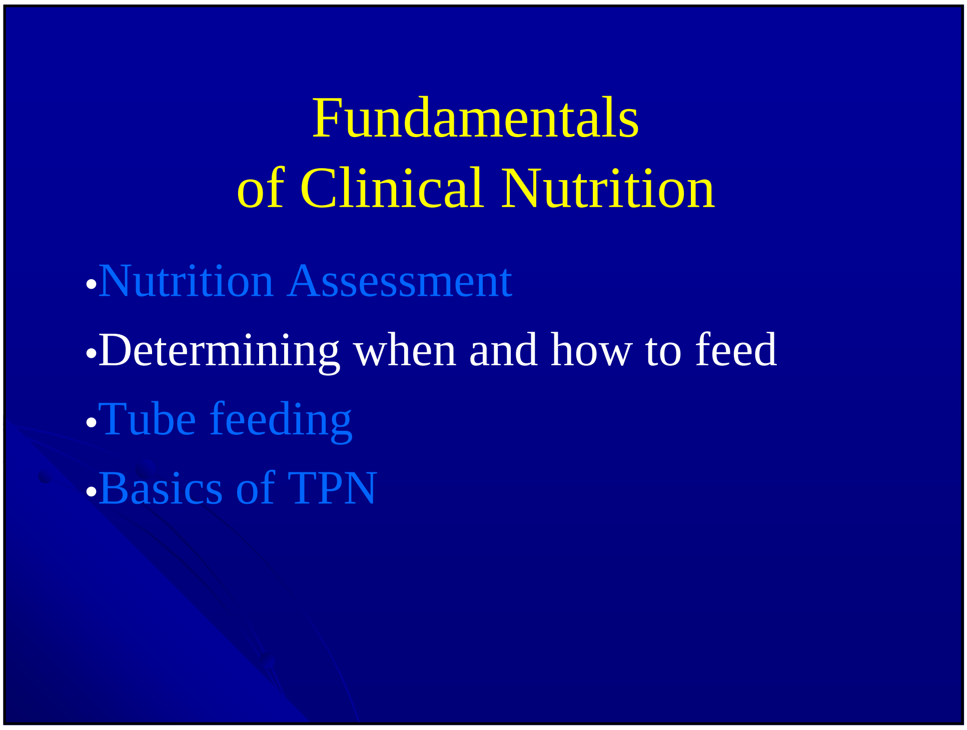
Why Metabolic Cart Studies May Be Inaccurate

- All exhaled gas is not collected
  - Leaks around the tracheostomy tube cuff
  - Chest tubes
- Measurements made during dialysis
  - The CO_2 is dialyzed off
- Nitric Oxide therapy
- Steady state not achieved



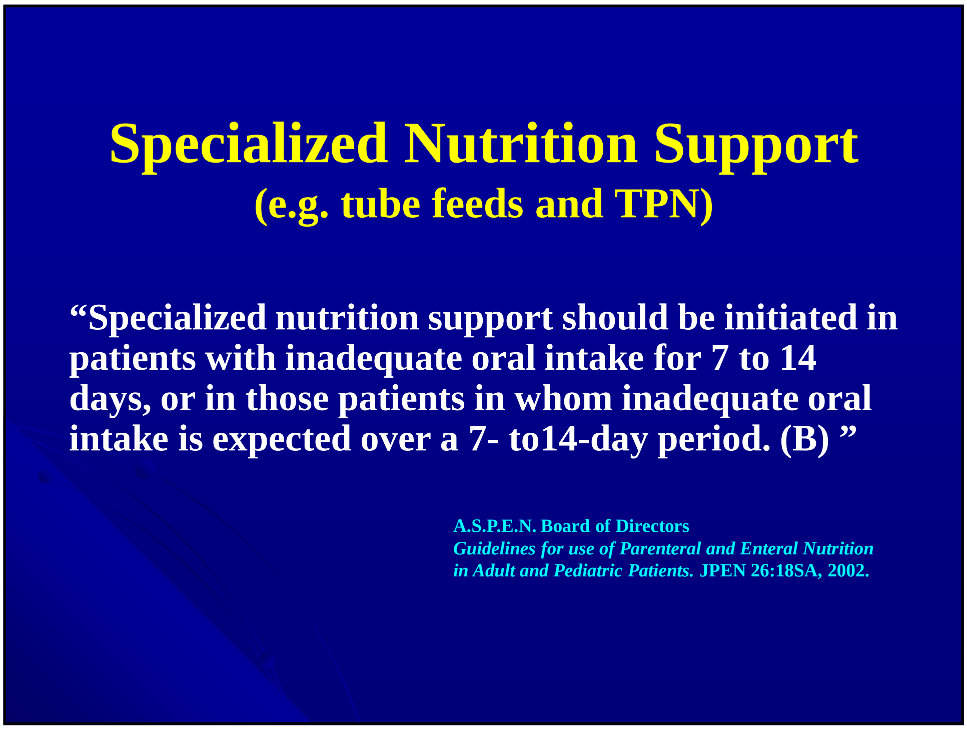
Nutrition Assessment:
Determining Daily Protein Needs

Condition	gms/kg/day
Non-hypermetabolic/Well nourished	1.0-1.3
Hypermetabolic and/or Protein-Calorie Malnutrition	1.2-1.5
Nitrogen retention disorders (liver, kidney)	0.5-1.0
Burn, >20% TBSA burn	2.0
Burn, <20% TBSA burn	1.5
High dose steroids	1.5
Hemodialysis (maintenance)	1.1-1.2
Hemodialysis (undernourished)	1.2-1.4
Peritoneal Dialysis (maintenance)	1.2-1.5
Peritoneal Dialysis (undernourished)	1.5-1.6



Fundamentals
of Clinical Nutrition

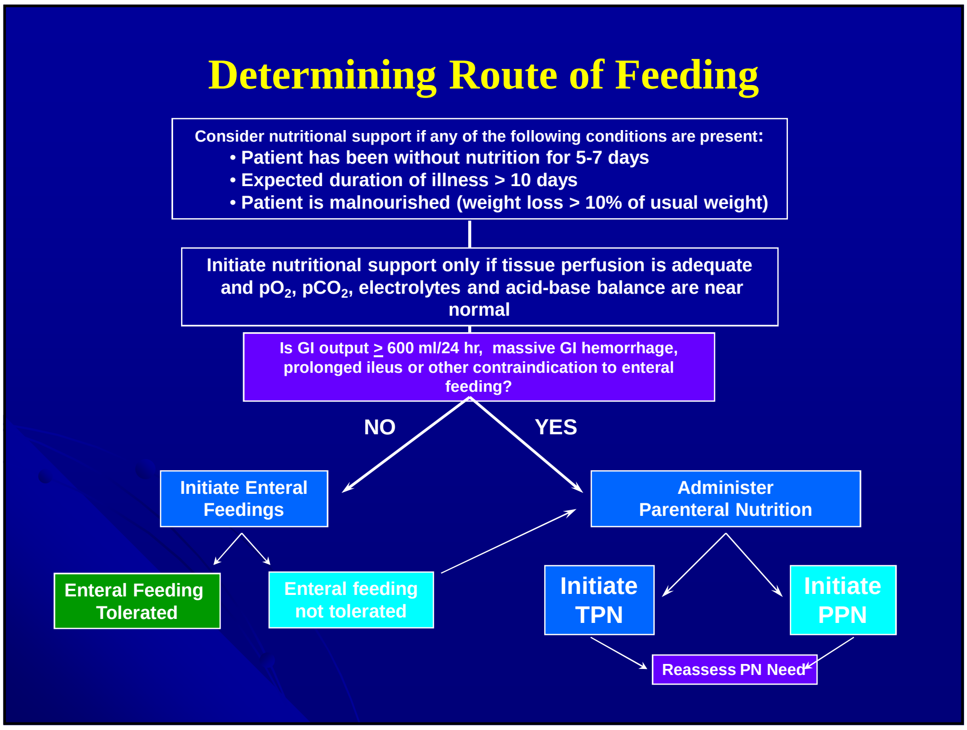
- Nutrition Assessment
- Determining when and how to feed
- Tube feeding
- Basics of TPN



Specialized Nutrition Support
(e.g. tube feeds and TPN)

"Specialized nutrition support should be initiated in patients with inadequate oral intake for 7 to 14 days, or in those patients in whom inadequate oral intake is expected over a 7- to14-day period. (B) "

A.S.P.E.N. Board of Directors
Guidelines for use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. JPEN 26:18SA, 2002.



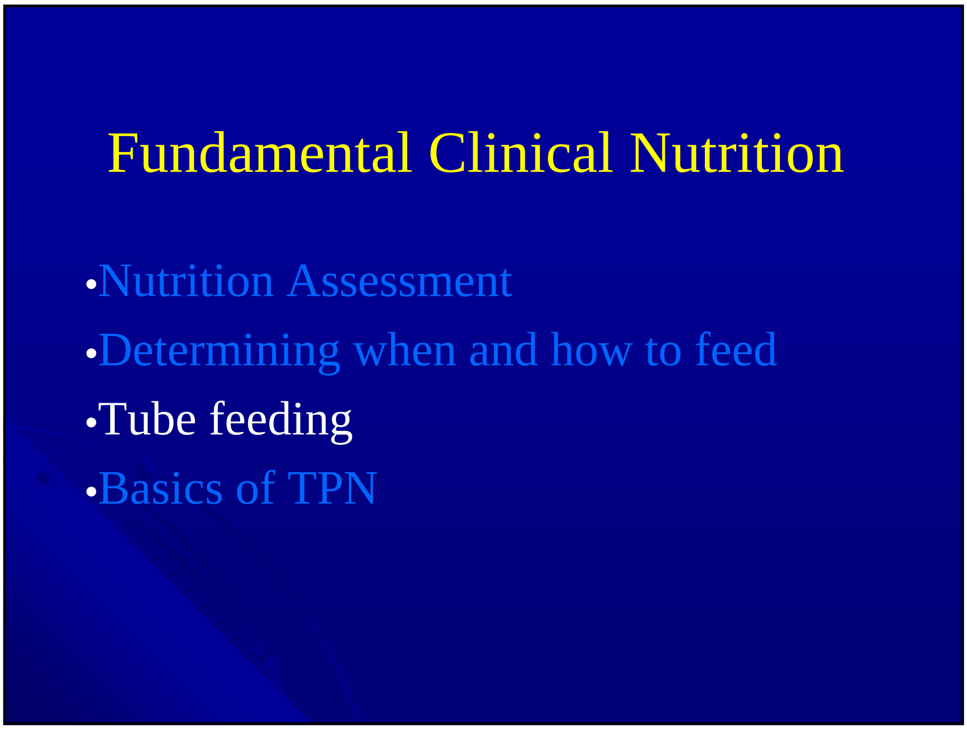
Determining Route of Feeding

Consider nutritional support if any of the following conditions are present:
- Patient has been without nutrition for 5-7 days
- Expected duration of illness > 10 days
- Patient is malnourished (weight loss > 10% of usual weight)

Initiate nutritional support only if tissue perfusion is adequate and pO_2, pCO_2, electrolytes and acid-base balance are near normal

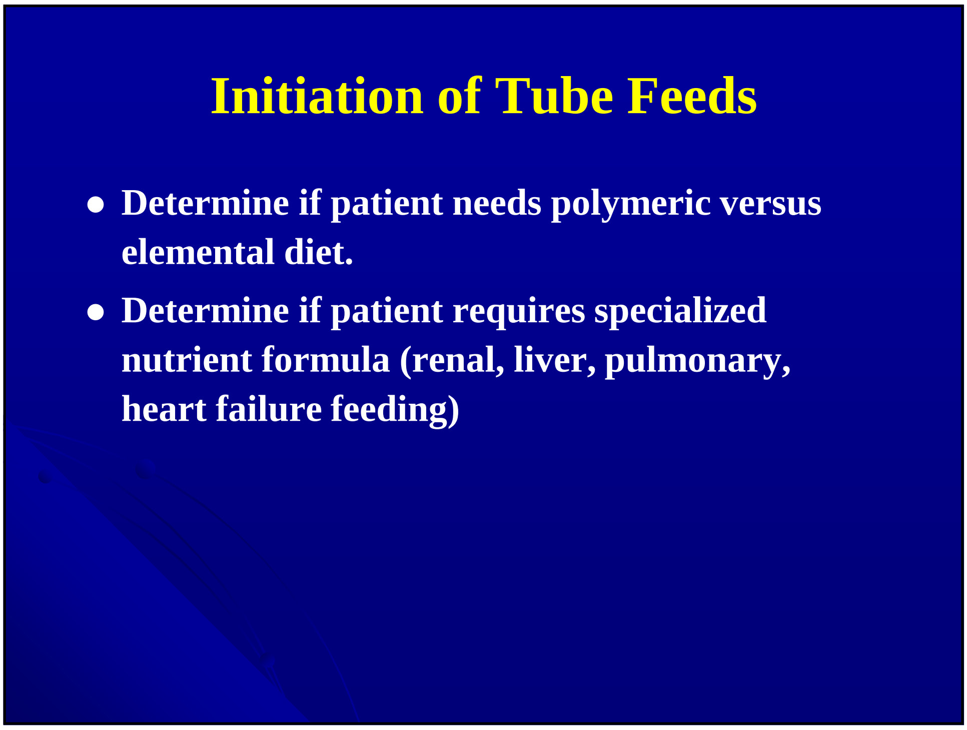
Is GI output $\geq$ 600 ml/24 hr, massive GI hemorrhage, prolonged ileus or other contraindication to enteral feeding?

NO
YES
Initiate Enteral Feedings
Administer Parenteral Nutrition
Enteral Feeding Tolerated
Enteral feeding not tolerated
Initiate TPN
Initiate PPN
Reassess PN Need



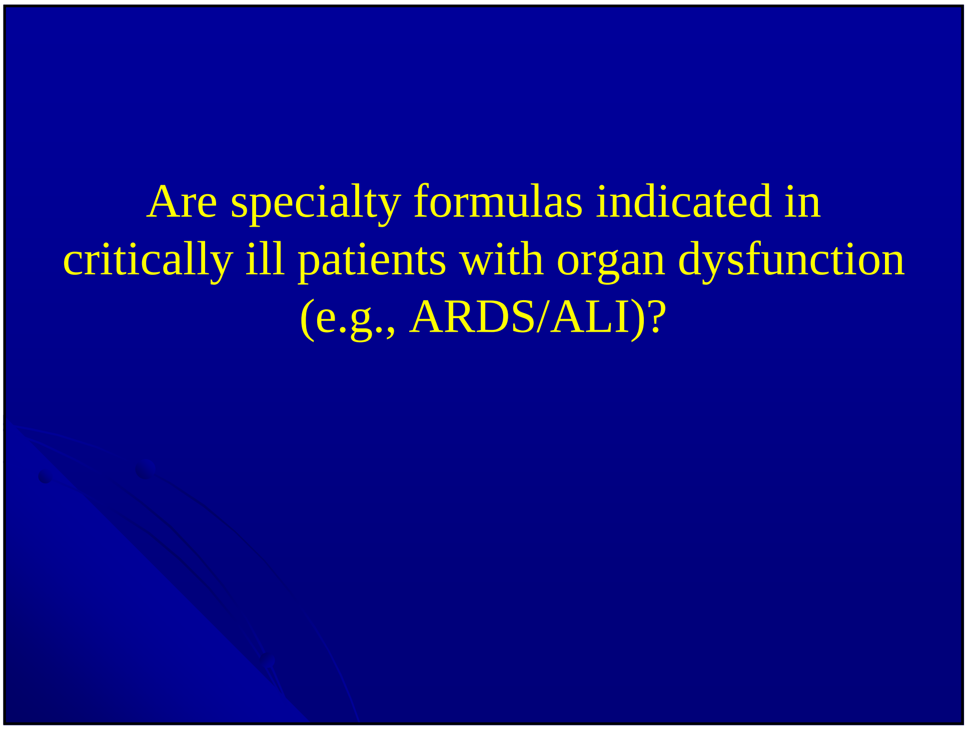
Fundamental Clinical Nutrition

- Nutrition Assessment
- Determining when and how to feed
- Tube feeding
- Basics of TPN

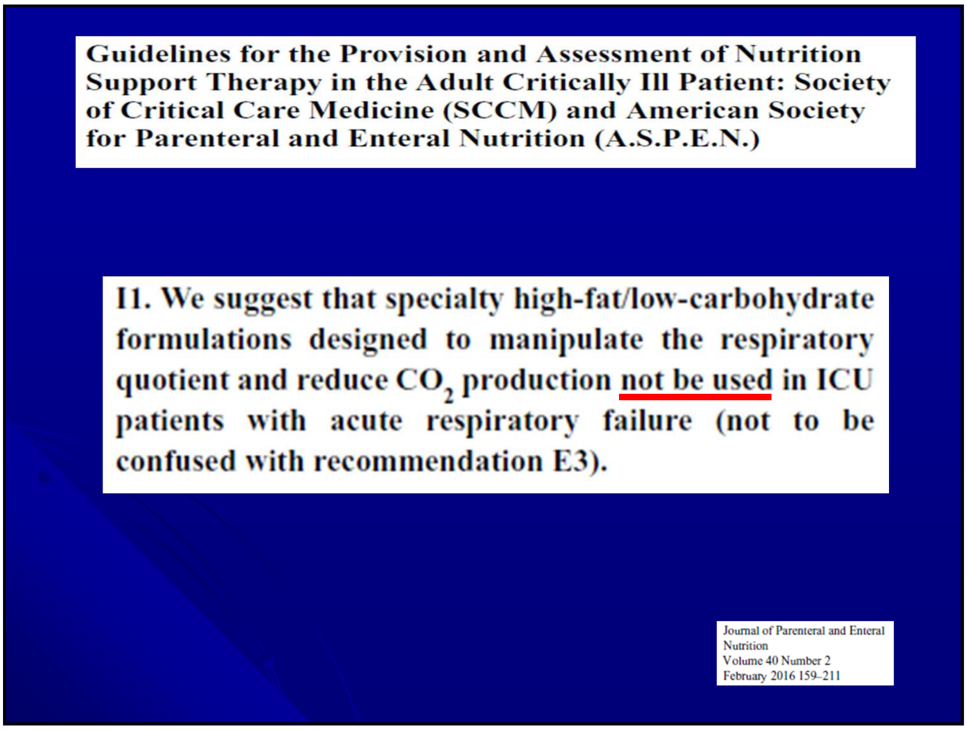


Initiation of Tube Feeds

- **Determine if patient needs polymeric versus elemental diet.**
- **Determine if patient requires specialized nutrient formula (renal, liver, pulmonary, heart failure feeding)**



Are specialty formulas indicated in critically ill patients with organ dysfunction (e.g., ARDS/ALI)?



Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

I1. We suggest that specialty high-fat/low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce CO_2 production not be used in ICU patients with acute respiratory failure (not to be confused with recommendation E3).

Journal of Parenteral and Enteral Nutrition
Volume 40 Number 2
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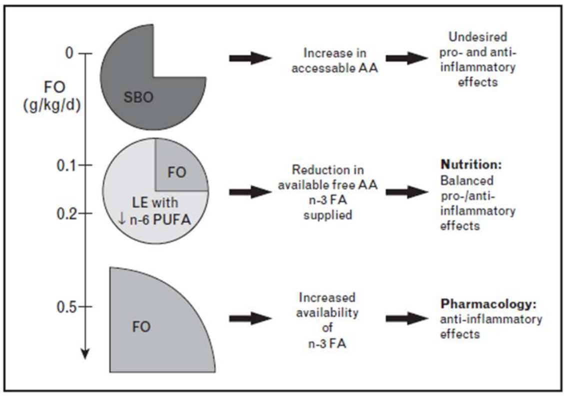
Should ALI/ARDS Patients receive an anti-inflammatory lipid EN formula with antioxidants ?

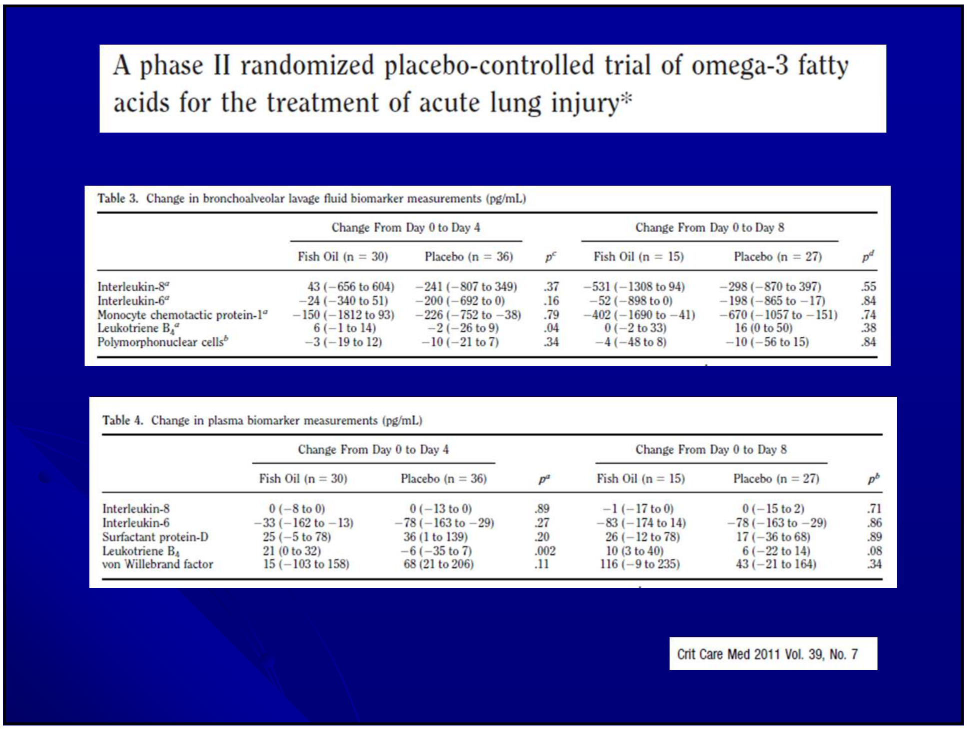
Fish oil in critical illness

Konstantin Mayer and Werner Seeger

Figure 1 Effects of different amounts of fish oil-based lipid emulsions supplied to critical ill patients


0
FO
(g/kg/d)
SBO
Increase in accessable AA
Undesired pro- and anti-inflammatory effects
0.1
FO
LE with ↓ n-6 PUFA
0.2
Reduction in available free AA n-3 FA supplied
Nutrition: Balanced pro-/anti-inflammatory effects
0.5
FO
Increased availability of n-3 FA
Pharmacology: anti-inflammatory effects

Current Opinion in Clinical Nutrition and Metabolic Care 2008, 11:121–127



A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury*

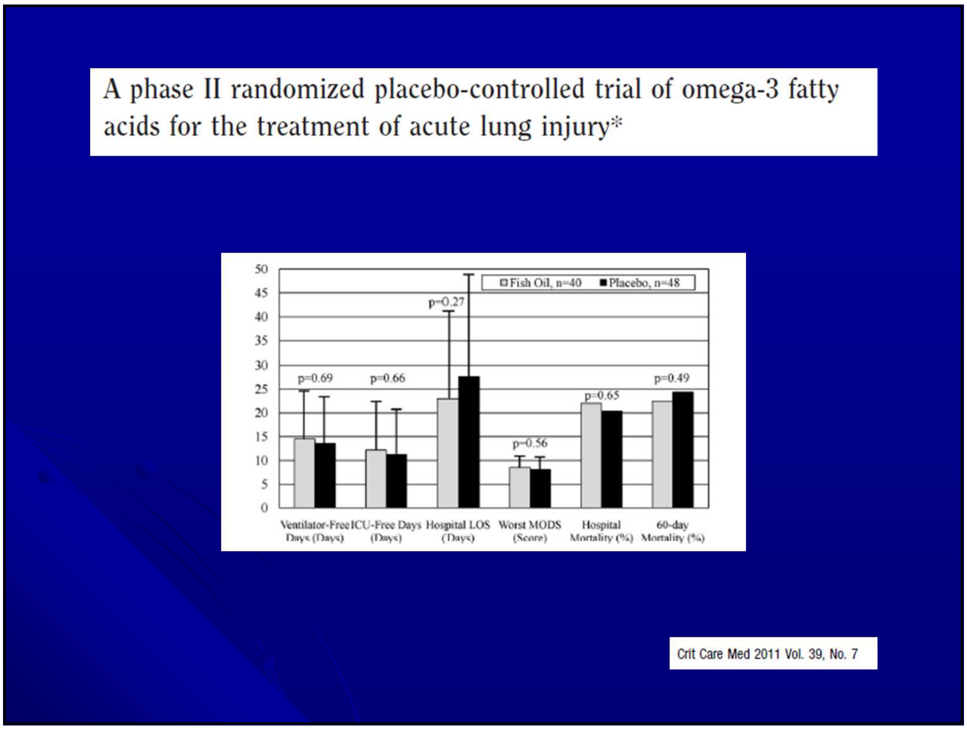
Table 3. Change in bronchoalveolar lavage fluid biomarker measurements (pg/mL)

	Change From Day 0 to Day 4			Change From Day 0 to Day 8		
	Fish Oil (n = 30)	Placebo (n = 36)	p^c	Fish Oil (n = 15)	Placebo (n = 27)	p^d
Interleukin-8^a	43 (−656 to 604)	−241 (−807 to 349)	.37	−531 (−1308 to 94)	−298 (−870 to 397)	.55
Interleukin-6^a	−24 (−340 to 51)	−200 (−692 to 0)	.16	−52 (−898 to 0)	−198 (−865 to −17)	.84
Monocyte chemotactic protein-1^a	−150 (−1812 to 93)	−226 (−752 to −38)	.79	−402 (−1690 to −41)	−670 (−1057 to −151)	.74
Leukotriene $B_4{}^a$	6 (−1 to 14)	−2 (−26 to 9)	.04	0 (−2 to 33)	16 (0 to 50)	.38
Polymorphonuclear cells^b	−3 (−19 to 12)	−10 (−21 to 7)	.34	−4 (−48 to 8)	−10 (−56 to 15)	.84

Table 4. Change in plasma biomarker measurements (pg/mL)

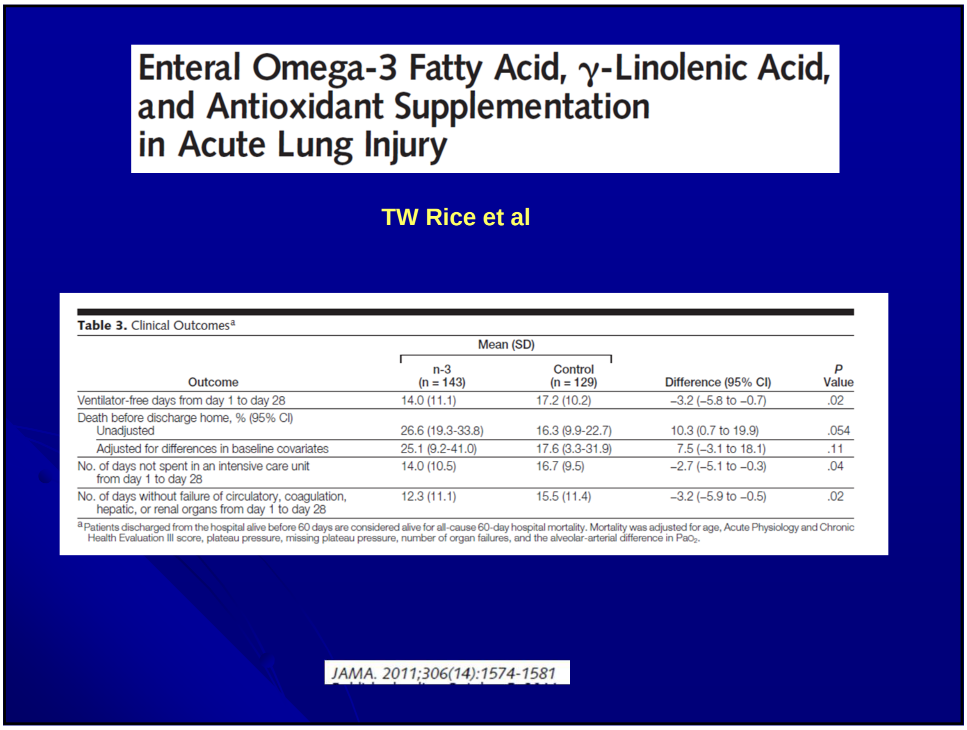
	Change From Day 0 to Day 4			Change From Day 0 to Day 8		
	Fish Oil (n = 30)	Placebo (n = 36)	p^a	Fish Oil (n = 15)	Placebo (n = 27)	p^b
Interleukin-8	0 (−8 to 0)	0 (−13 to 0)	.89	−1 (−17 to 0)	0 (−15 to 2)	.71
Interleukin-6	−33 (−162 to −13)	−78 (−163 to −29)	.27	−83 (−174 to 14)	−78 (−163 to −29)	.86
Surfactant protein-D	25 (−5 to 78)	36 (1 to 139)	.20	26 (−12 to 78)	17 (−36 to 68)	.89
Leukotriene B_4	21 (0 to 32)	−6 (−35 to 7)	.002	10 (3 to 40)	6 (−22 to 14)	.08
von Willebrand factor	15 (−103 to 158)	68 (21 to 206)	.11	116 (−9 to 235)	43 (−21 to 164)	.34

Crit Care Med 2011 Vol. 39, No. 7



A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury*

Crit Care Med 2011 Vol. 39, No. 7



Enteral Omega-3 Fatty Acid, γ-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury

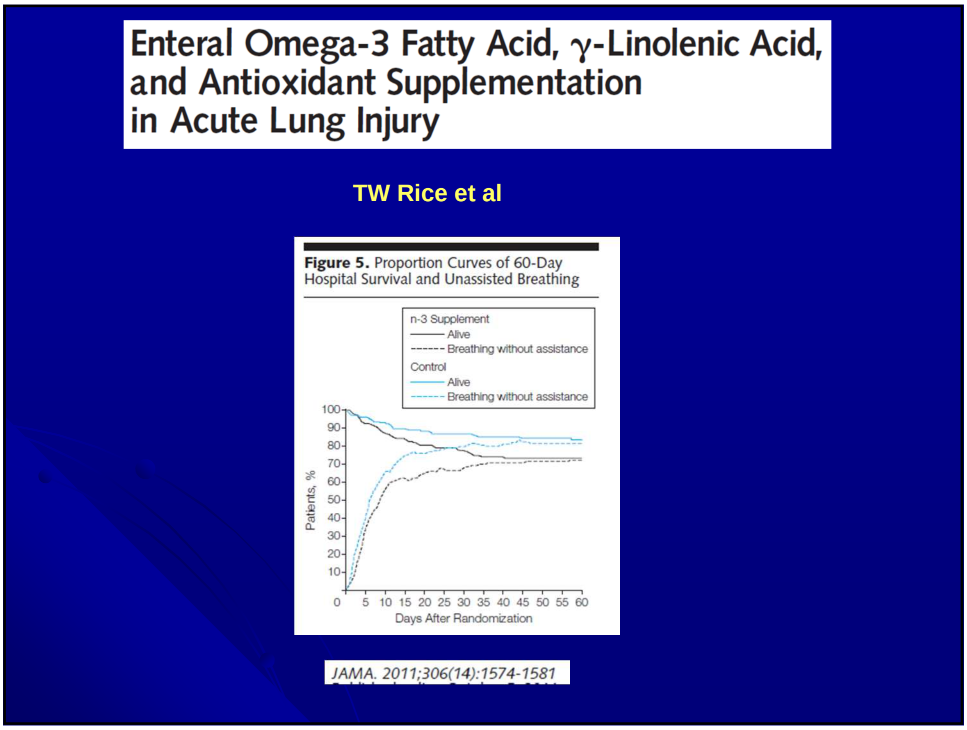
TW Rice et al

Table 3. Clinical Outcomes[a]

Outcome	Mean (SD) n-3 (n = 143)	Mean (SD) Control (n = 129)	Difference (95% CI)	*P* Value
Ventilator-free days from day 1 to day 28	14.0 (11.1)	17.2 (10.2)	–3.2 (–5.8 to –0.7)	.02
Death before discharge home, % (95% CI)				
Unadjusted	26.6 (19.3-33.8)	16.3 (9.9-22.7)	10.3 (0.7 to 19.9)	.054
Adjusted for differences in baseline covariates	25.1 (9.2-41.0)	17.6 (3.3-31.9)	7.5 (–3.1 to 18.1)	.11
No. of days not spent in an intensive care unit from day 1 to day 28	14.0 (10.5)	16.7 (9.5)	–2.7 (–5.1 to –0.3)	.04
No. of days without failure of circulatory, coagulation, hepatic, or renal organs from day 1 to day 28	12.3 (11.1)	15.5 (11.4)	–3.2 (–5.9 to –0.5)	.02

[a] Patients discharged from the hospital alive before 60 days are considered alive for all-cause 60-day hospital mortality. Mortality was adjusted for age, Acute Physiology and Chronic Health Evaluation III score, plateau pressure, missing plateau pressure, number of organ failures, and the alveolar-arterial difference in PaO_2.

JAMA. 2011;306(14):1574-1581

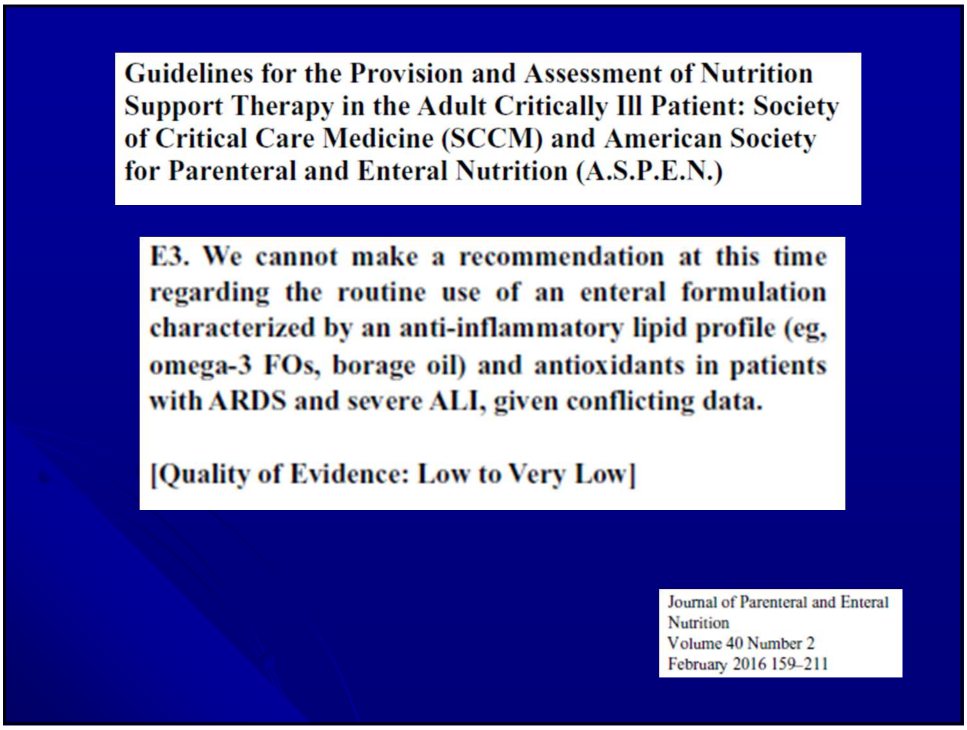


Enteral Omega-3 Fatty Acid, γ-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury

TW Rice et al

Figure 5. Proportion Curves of 60-Day Hospital Survival and Unassisted Breathing

JAMA. 2011;306(14):1574-1581



Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

E3. We cannot make a recommendation at this time regarding the routine use of an enteral formulation characterized by an anti-inflammatory lipid profile (eg, omega-3 FOs, borage oil) and antioxidants in patients with ARDS and severe ALI, given conflicting data.

[Quality of Evidence: Low to Very Low]

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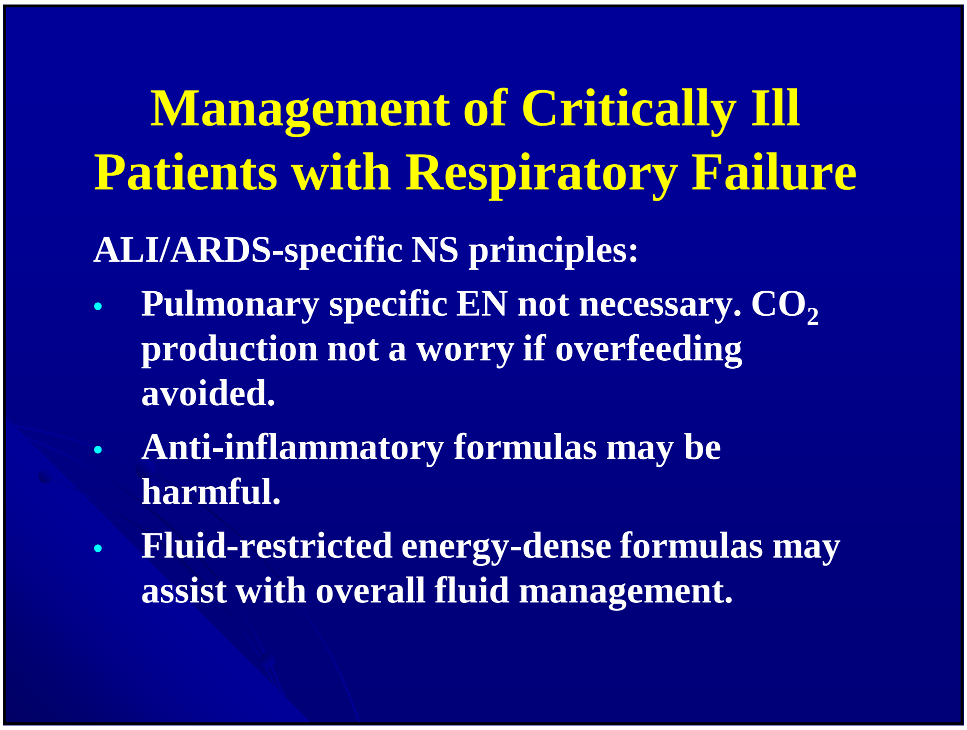

Management of Critically Ill Patients with Respiratory Failure

ALI/ARDS-specific NS principles:

- Pulmonary specific EN not necessary. CO_2 production not a worry if overfeeding avoided.
- Anti-inflammatory formulas may be harmful.
- Fluid-restricted energy-dense formulas may assist with overall fluid management.

Are specialty formulas indicated in critically ill patients with organ dysfunction (e.g., ARDS/ALI)?

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

E1. Based on expert consensus, we suggest using a standard polymeric formula when initiating EN in the ICU setting. We suggest avoiding the routine use of all specialty formulas in critically ill patients in a MICU and disease-specific formulas in the SICU.

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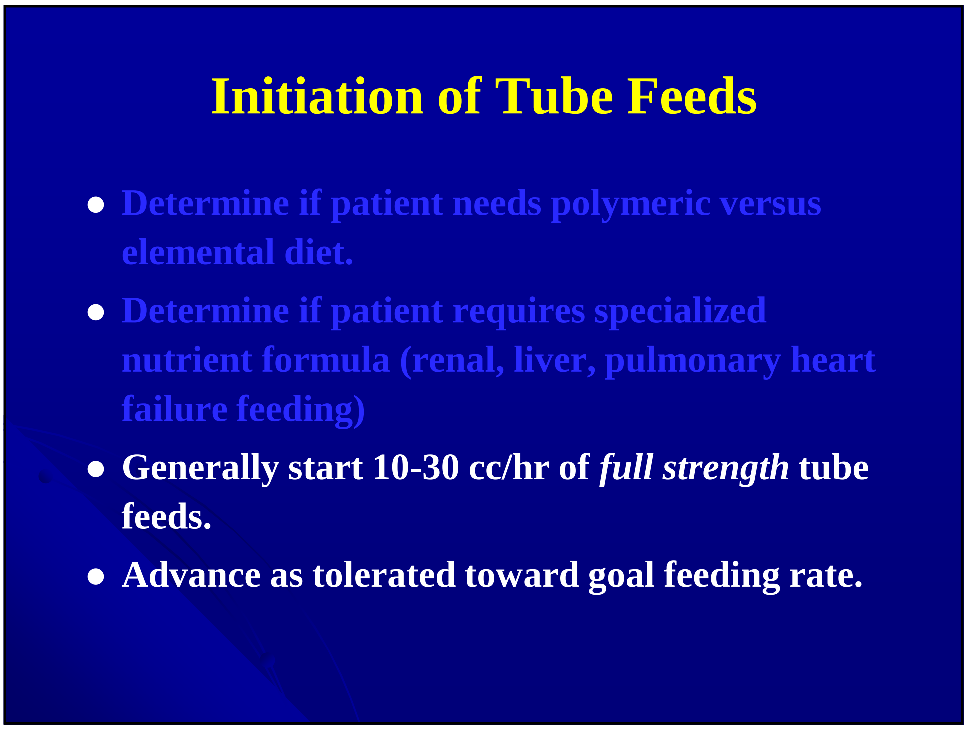
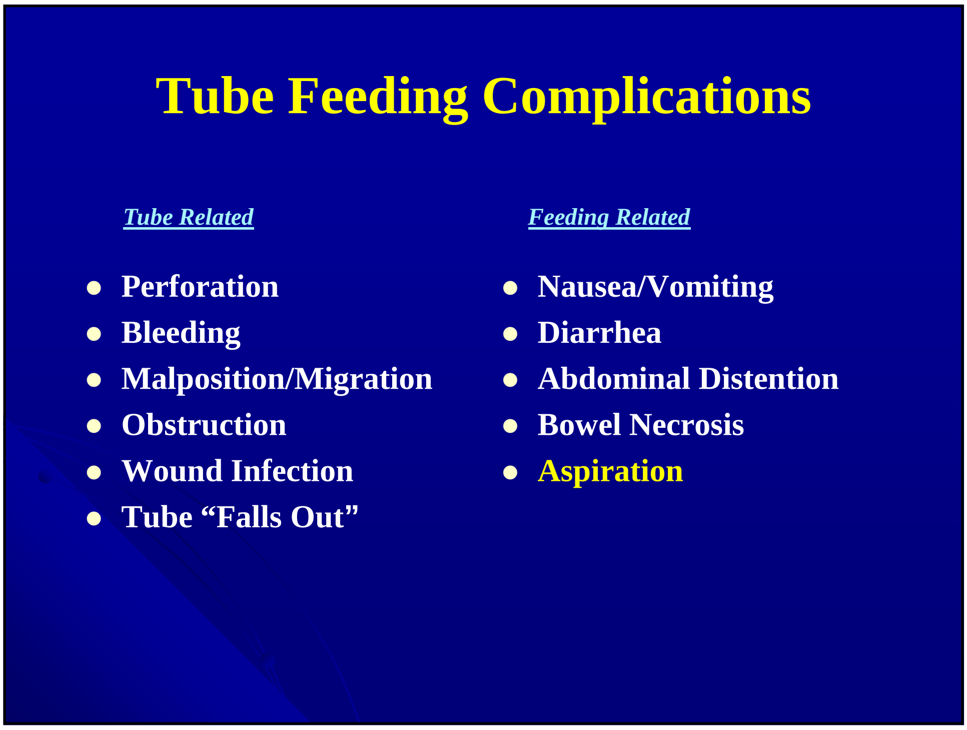


Initiation of Tube Feeds

- Determine if patient needs polymeric versus elemental diet.
- Determine if patient requires specialized nutrient formula (renal, liver, pulmonary heart failure feeding)
- Generally start 10-30 cc/hr of *full strength* tube feeds.
- Advance as tolerated toward goal feeding rate.



Tube Feeding Complications

Tube Related

- Perforation
- Bleeding
- Malposition/Migration
- Obstruction
- Wound Infection
- Tube “Falls Out”

Feeding Related

- Nausea/Vomiting
- Diarrhea
- Abdominal Distention
- Bowel Necrosis
- Aspiration

Aspiration of Tube Feeds

Increased Risk

- Sedation
- Altered Sensorium
- Patient Location
- Use of Certain Drugs

Decreased Risk

- HOB Elevated 30-45°
- Place tube postpyloric or in jejunum
- ? Prokinetic Agents

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

D4d. Based on expert consensus, we suggest that nursing directives to reduce risk of aspiration and VAP be employed. In all intubated ICU patients receiving EN, the head of the bed should be elevated 30°–45° and use of chlorhexidine mouthwash twice a day should be considered.

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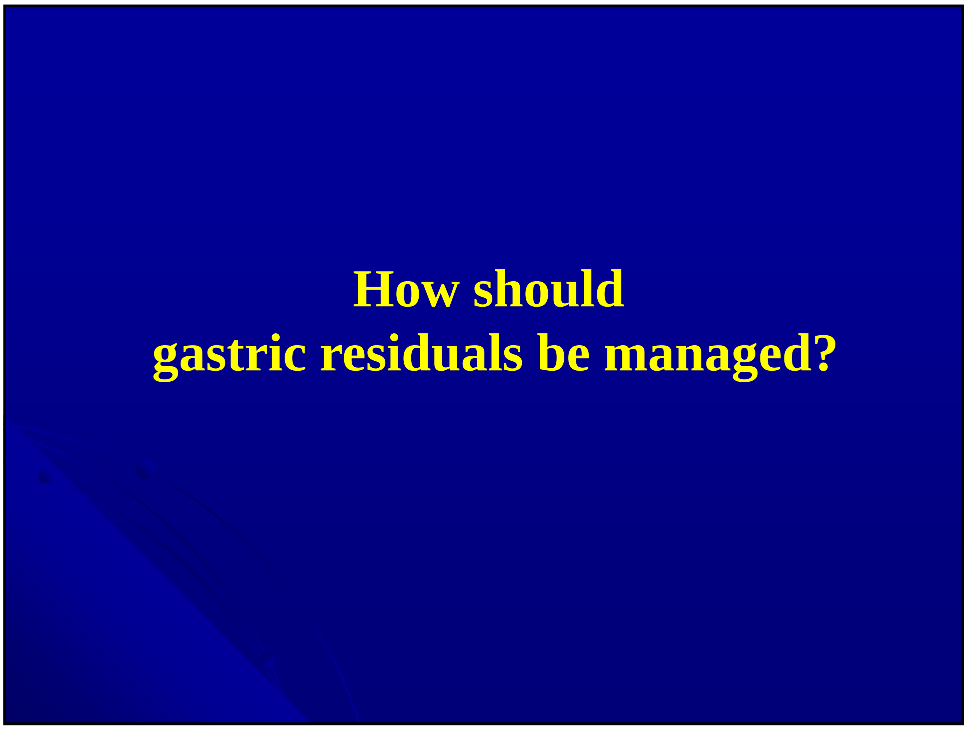
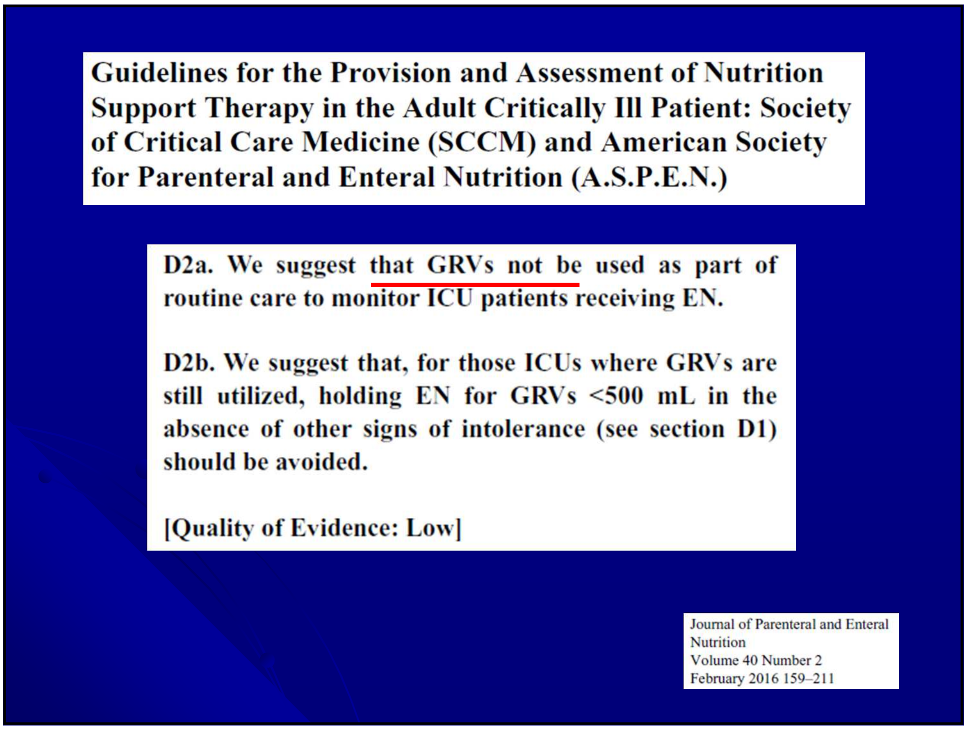


How should gastric residuals be managed?



Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

D2a. We suggest that GRVs not be used as part of routine care to monitor ICU patients receiving EN.

D2b. We suggest that, for those ICUs where GRVs are still utilized, holding EN for GRVs <500 mL in the absence of other signs of intolerance (see section D1) should be avoided.

[Quality of Evidence: Low]

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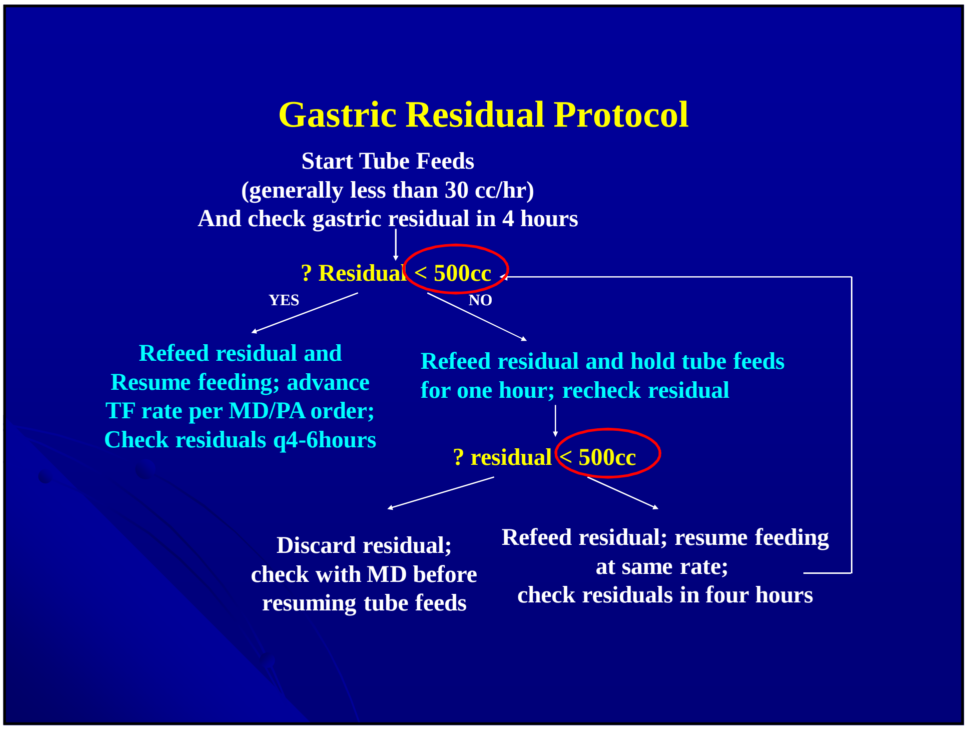


Gastric Residual Protocol

Start Tube Feeds
(generally less than 30 cc/hr)
And check gastric residual in 4 hours

? Residual < 500cc

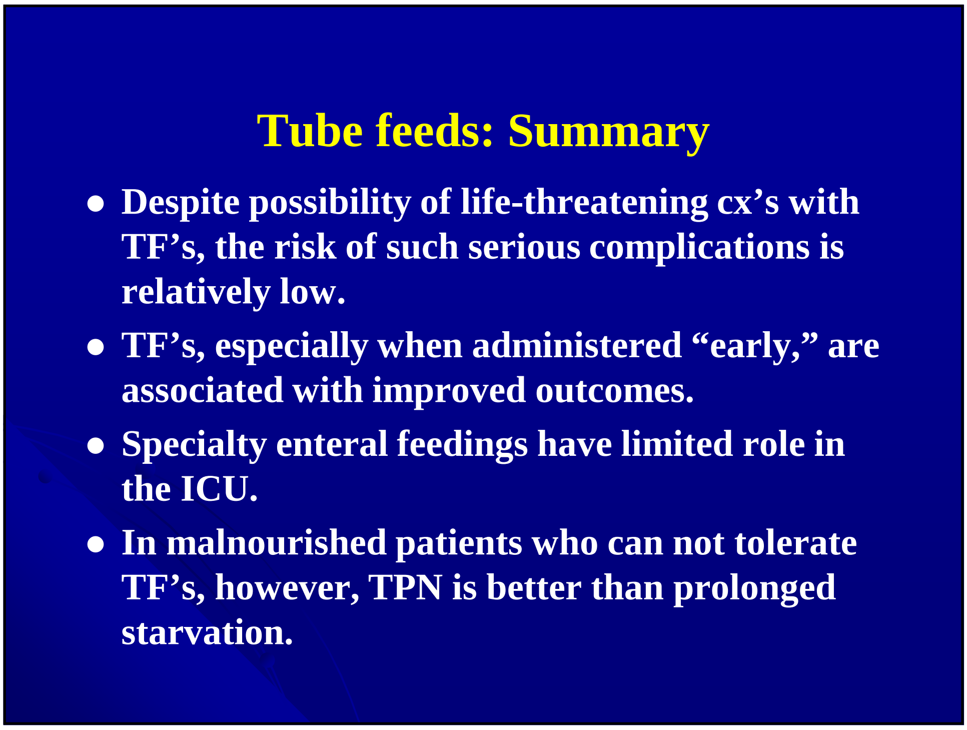
Refeed residual and
Resume feeding; advance
TF rate per MD/PA order;
Check residuals q4-6hours

Refeed residual and hold tube feeds
for one hour; recheck residual

? residual < 500cc

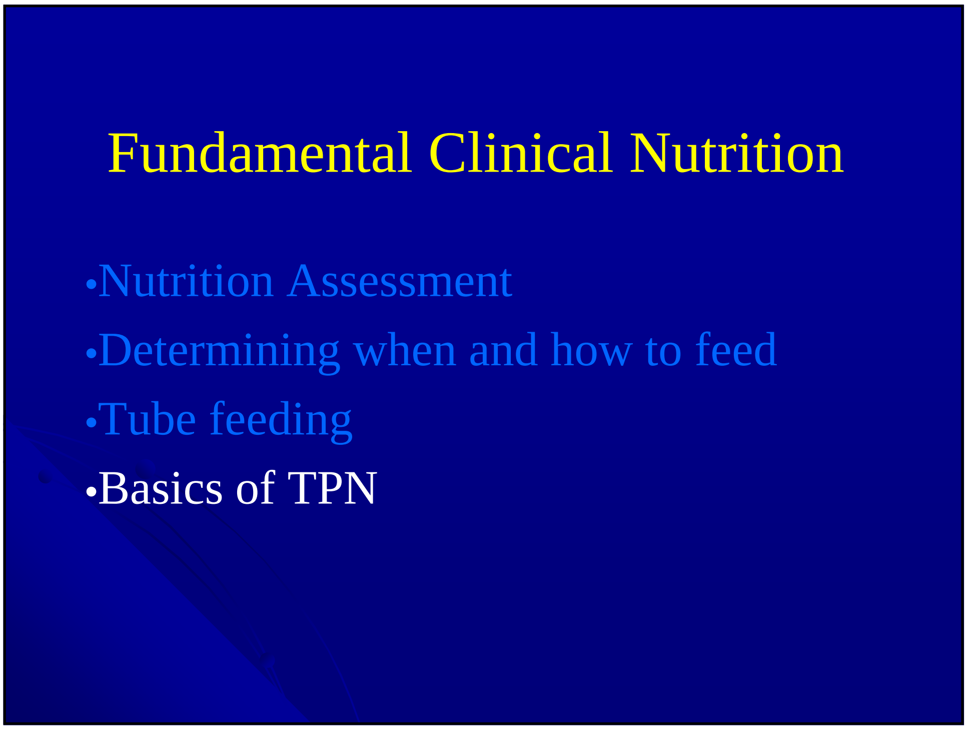
Discard residual;
check with MD before
resuming tube feeds

Refeed residual; resume feeding
at same rate;
check residuals in four hours



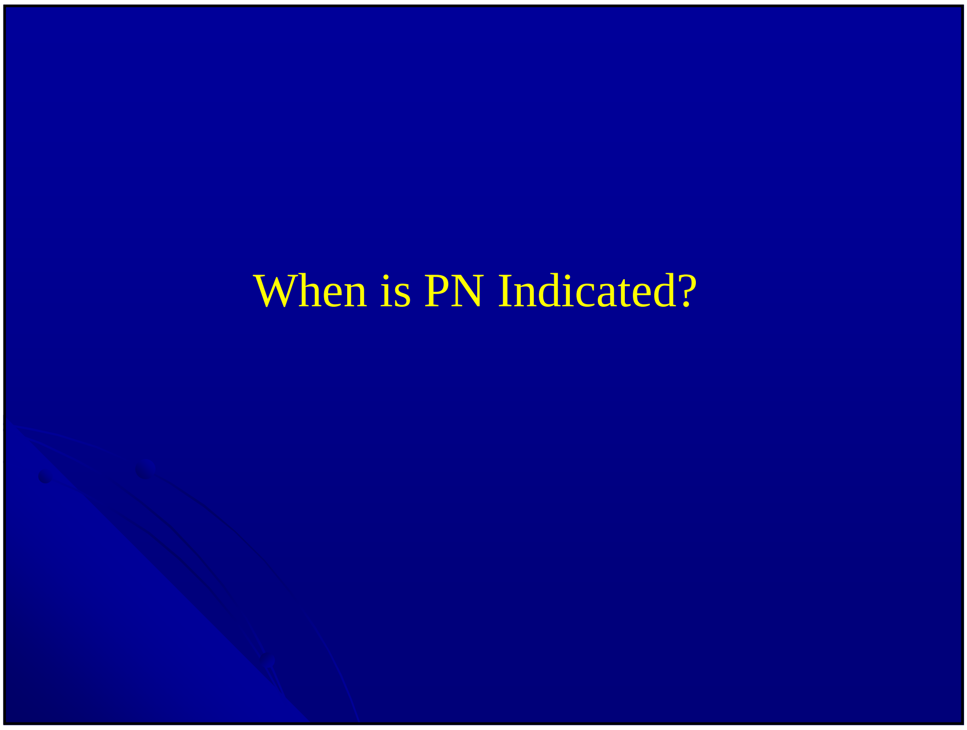
Tube feeds: Summary

- Despite possibility of life-threatening cx’s with TF’s, the risk of such serious complications is relatively low.
- TF’s, especially when administered “early,” are associated with improved outcomes.
- Specialty enteral feedings have limited role in the ICU.
- In malnourished patients who can not tolerate TF’s, however, TPN is better than prolonged starvation.

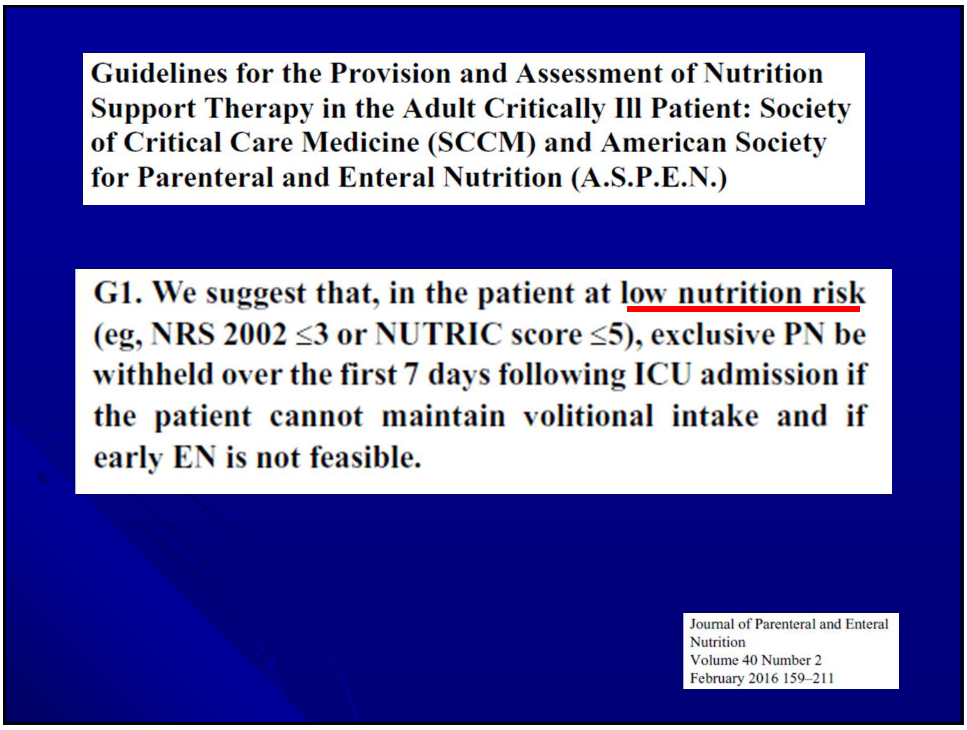


Fundamental Clinical Nutrition

- Nutrition Assessment
- Determining when and how to feed
- Tube feeding
- Basics of TPN



When is PN Indicated?



Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

G1. We suggest that, in the patient at low nutrition risk (eg, NRS 2002 ≤3 or NUTRIC score ≤5), exclusive PN be withheld over the first 7 days following ICU admission if the patient cannot maintain volitional intake and if early EN is not feasible.

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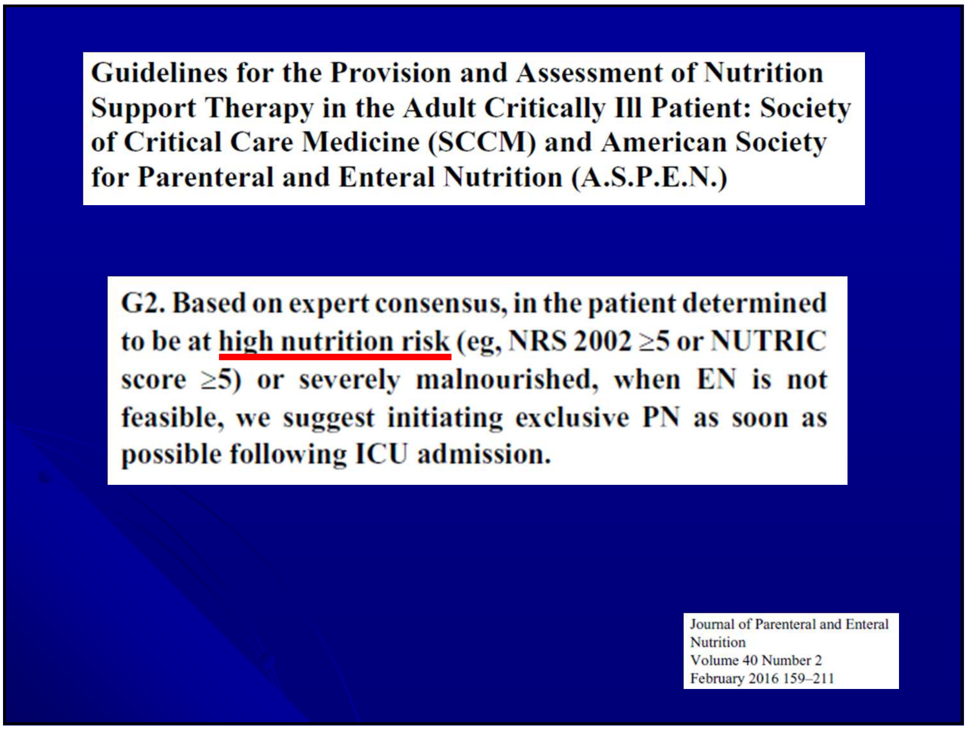

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

G2. Based on expert consensus, in the patient determined to be at high nutrition risk (eg, NRS 2002 ≥5 or NUTRIC score ≥5) or severely malnourished, when EN is not feasible, we suggest initiating exclusive PN as soon as possible following ICU admission.

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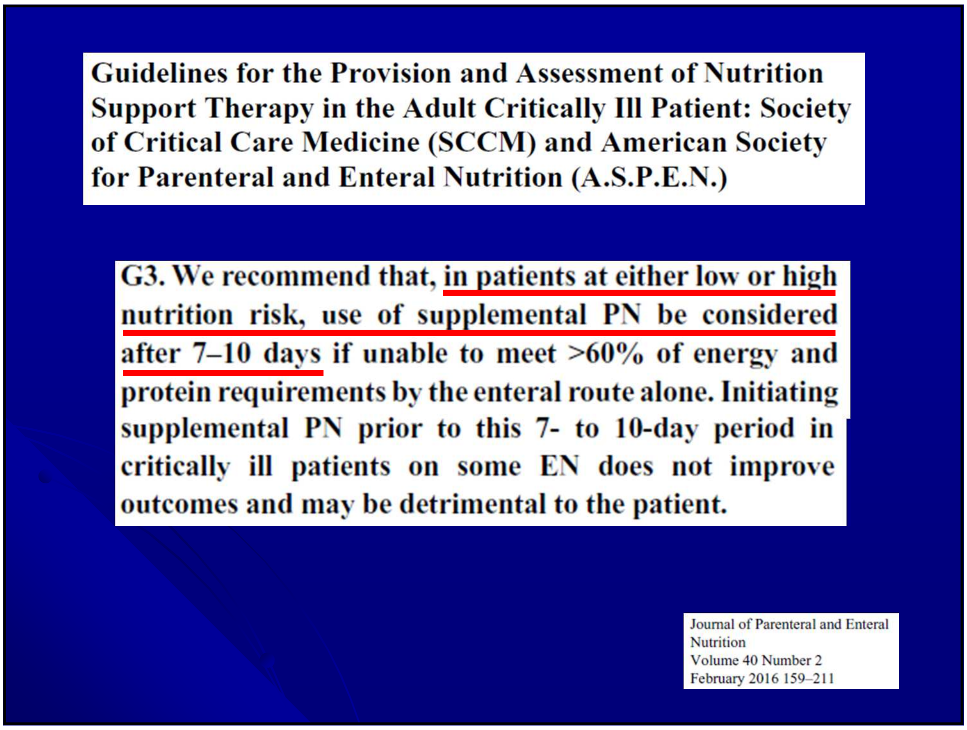

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

G3. We recommend that, in patients at either low or high nutrition risk, use of supplemental PN be considered after 7–10 days if unable to meet >60% of energy and protein requirements by the enteral route alone. Initiating supplemental PN prior to this 7- to 10-day period in critically ill patients on some EN does not improve outcomes and may be detrimental to the patient.

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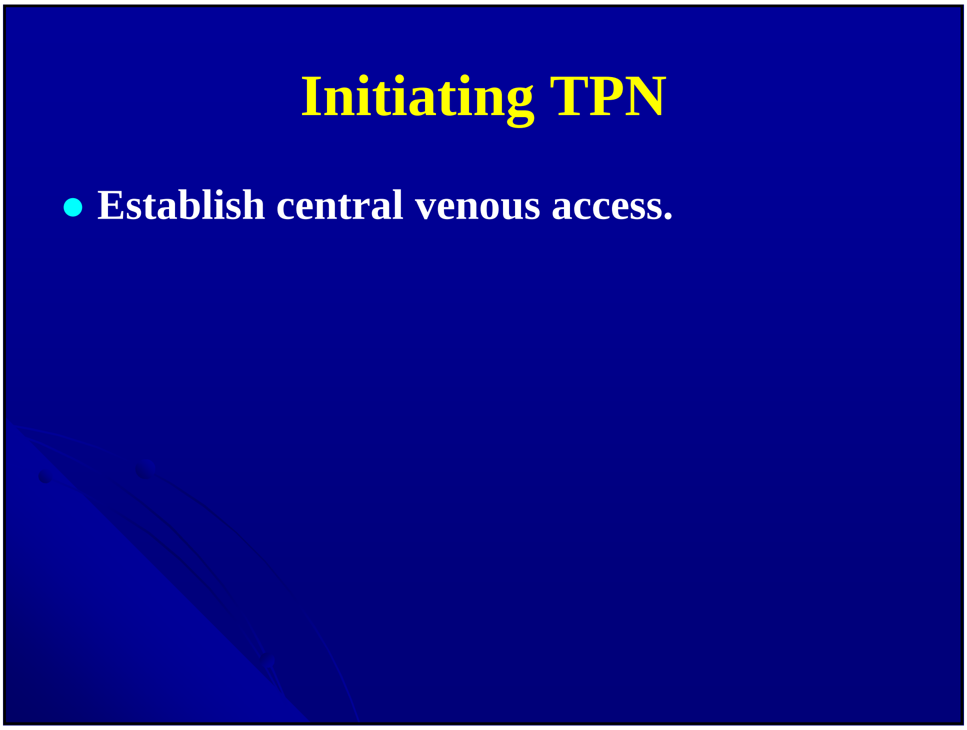
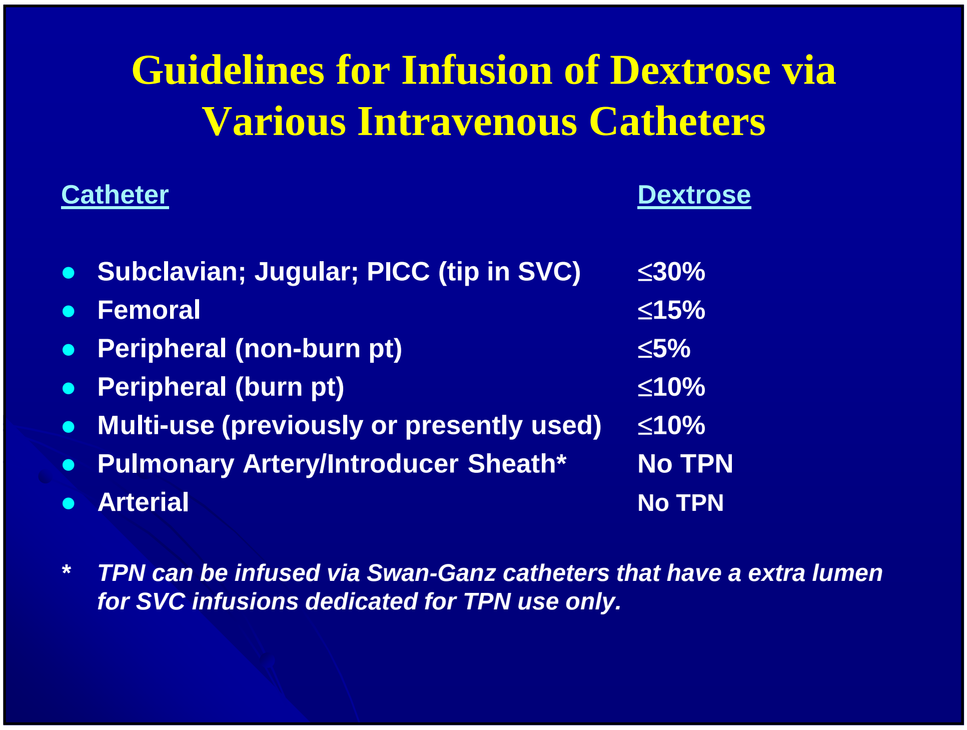


Initiating TPN

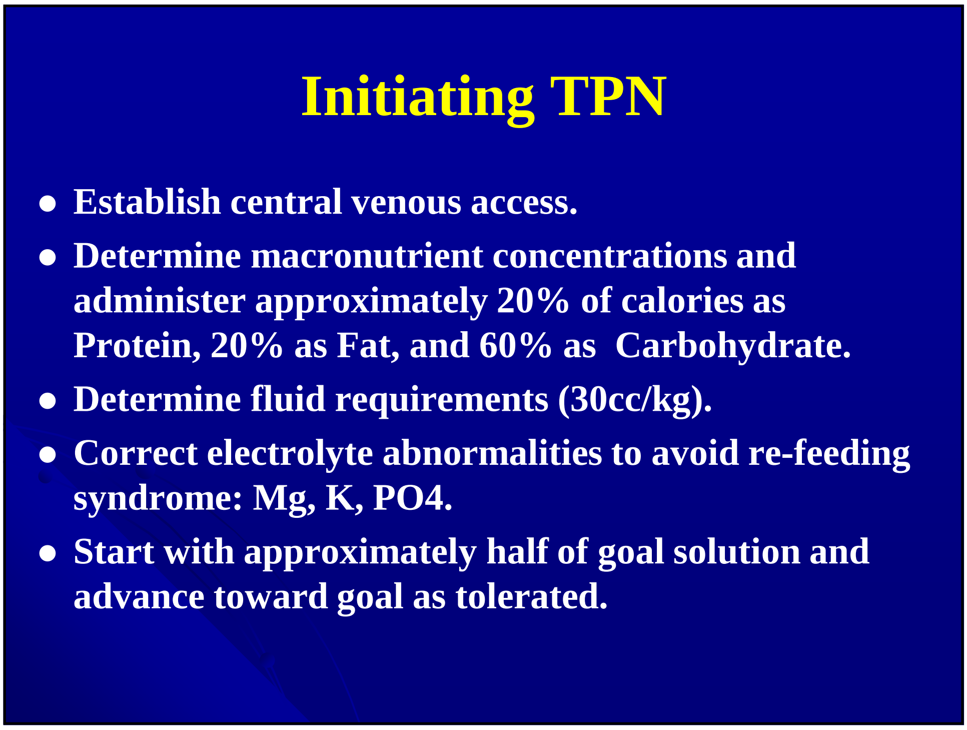
- Establish central venous access.



Guidelines for Infusion of Dextrose via Various Intravenous Catheters

Catheter	Dextrose
Subclavian; Jugular; PICC (tip in SVC)	≤30%
Femoral	≤15%
Peripheral (non-burn pt)	≤5%
Peripheral (burn pt)	≤10%
Multi-use (previously or presently used)	≤10%
Pulmonary Artery/Introducer Sheath*	No TPN
Arterial	No TPN

* *TPN can be infused via Swan-Ganz catheters that have a extra lumen for SVC infusions dedicated for TPN use only.*



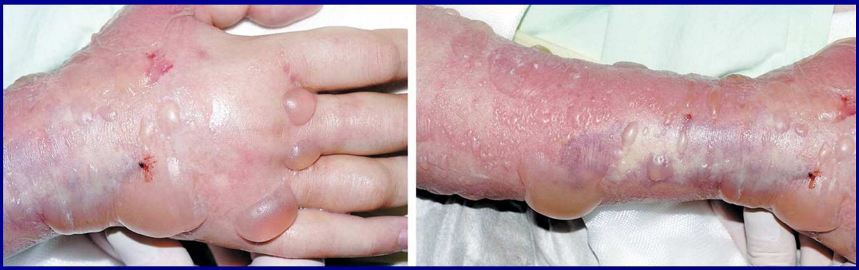
Initiating TPN

- Establish central venous access.
- Determine macronutrient concentrations and administer approximately 20% of calories as Protein, 20% as Fat, and 60% as Carbohydrate.
- Determine fluid requirements (30cc/kg).
- Correct electrolyte abnormalities to avoid re-feeding syndrome: Mg, K, PO4.
- Start with approximately half of goal solution and advance toward goal as tolerated.

Peripheral Parenteral Nutrition

- Useful on limited basis.
- Patient must be able to tolerate at least 2 liters of fluid per day.
- Two liters per day provides only 1040 calories.
- May supplement inadequate enteral feeding.
- Best used on short term basis.

Extravasation of Peripherally Administered Parenteral Nutrition

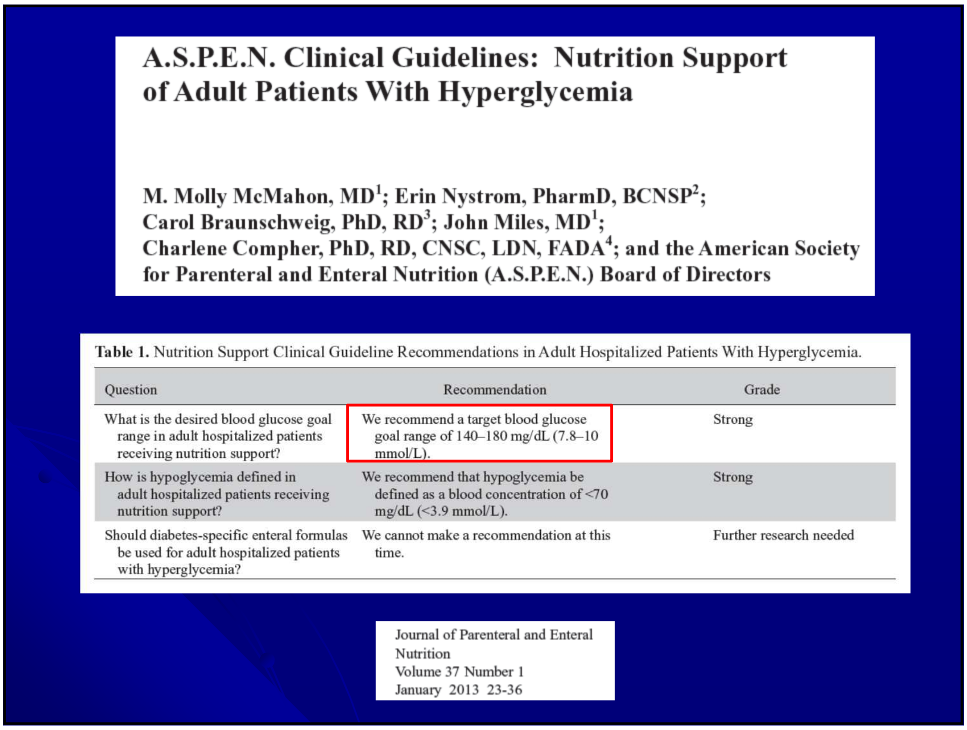


Belloni B, Andres C. N Engl J Med 2011;364:e20.

The NEW ENGLAND JOURNAL of MEDICINE

Common TPN-Associated Complications

- **Hyperglycemia**
- Hypoglycemia
- Electrolyte Abnormalities (Renal Failure)
- Refeeding Syndrome
- Infection



A.S.P.E.N. Clinical Guidelines: Nutrition Support of Adult Patients With Hyperglycemia

M. Molly McMahon, MD[1]; Erin Nystrom, PharmD, BCNSP[2];
Carol Braunschweig, PhD, RD[3]; John Miles, MD[1];
Charlene Compher, PhD, RD, CNSC, LDN, FADA[4]; and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors

Table 1. Nutrition Support Clinical Guideline Recommendations in Adult Hospitalized Patients With Hyperglycemia.

Question	Recommendation	Grade
What is the desired blood glucose goal range in adult hospitalized patients receiving nutrition support?	We recommend a target blood glucose goal range of 140–180 mg/dL (7.8–10 mmol/L).	Strong
How is hypoglycemia defined in adult hospitalized patients receiving nutrition support?	We recommend that hypoglycemia be defined as a blood concentration of <70 mg/dL (<3.9 mmol/L).	Strong
Should diabetes-specific enteral formulas be used for adult hospitalized patients with hyperglycemia?	We cannot make a recommendation at this time.	Further research needed

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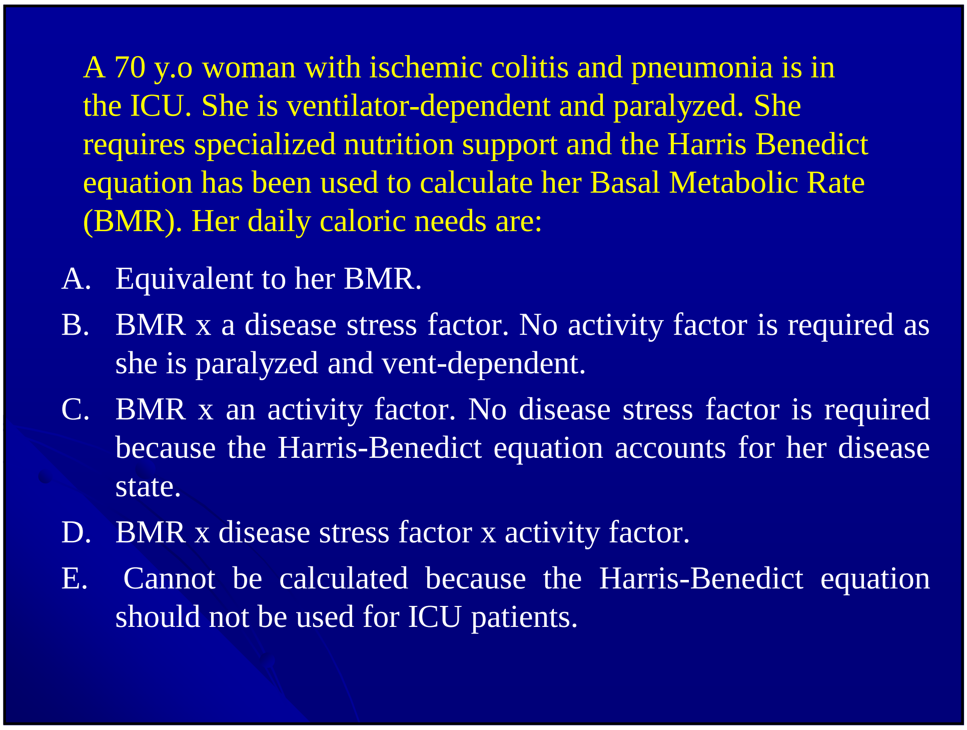
Clinical Nutrition: Summary and Conclusions

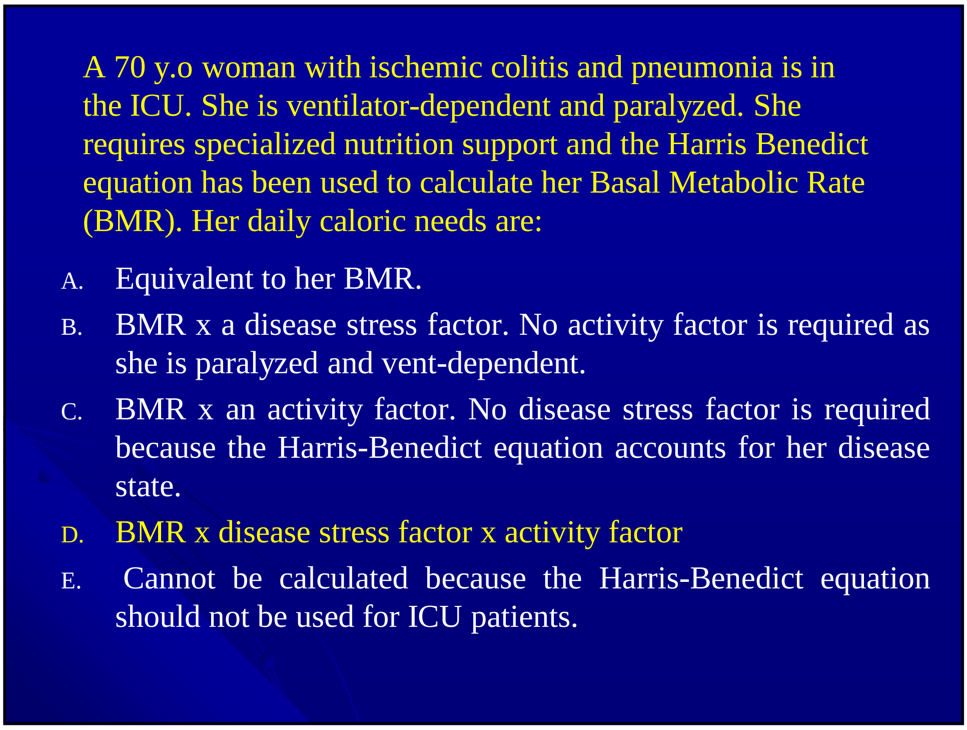
- Malnutrition is associated with increased morbidity, mortality and healthcare costs.
- Consider specialized nutrition support when oral intake is inadequate for extended periods.
- Enteral feeding is the preferred route of specialized nutrition support.
- Initiate TPN when the benefits outweigh the risks.
- Caveat: Nutrition can not overcome uncontrolled pathological processes.

Review Questions



A 70 y.o woman with ischemic colitis and pneumonia is in the ICU. She is ventilator-dependent and paralyzed. She requires specialized nutrition support and the Harris Benedict equation has been used to calculate her Basal Metabolic Rate (BMR). Her daily caloric needs are:

A. Equivalent to her BMR.
B. BMR x a disease stress factor. No activity factor is required as she is paralyzed and vent-dependent.
C. BMR x an activity factor. No disease stress factor is required because the Harris-Benedict equation accounts for her disease state.
D. BMR x disease stress factor x activity factor.
E. Cannot be calculated because the Harris-Benedict equation should not be used for ICU patients.



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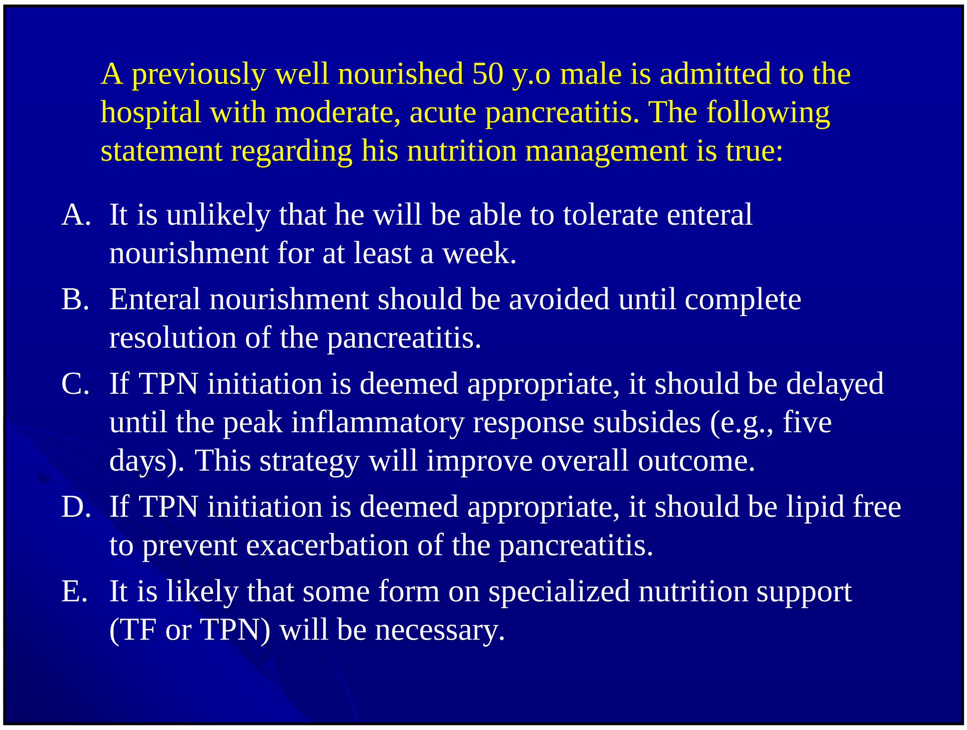
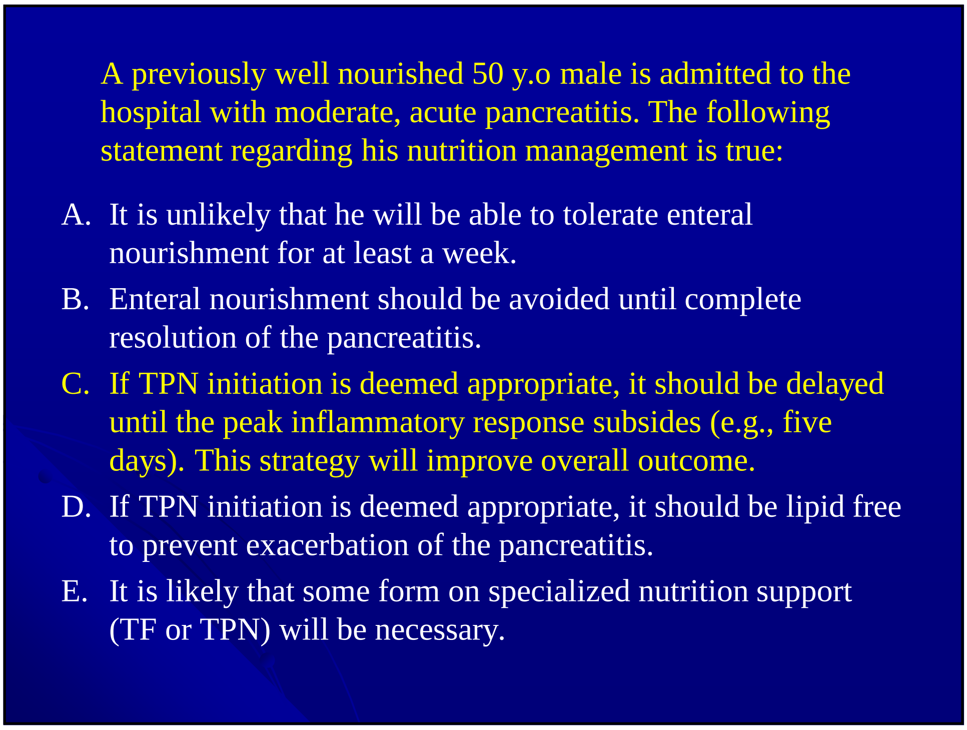


A previously well nourished 50 y.o male is admitted to the hospital with moderate, acute pancreatitis. The following statement regarding his nutrition management is true:

A. It is unlikely that he will be able to tolerate enteral nourishment for at least a week.
B. Enteral nourishment should be avoided until complete resolution of the pancreatitis.
C. If TPN initiation is deemed appropriate, it should be delayed until the peak inflammatory response subsides (e.g., five days). This strategy will improve overall outcome.
D. If TPN initiation is deemed appropriate, it should be lipid free to prevent exacerbation of the pancreatitis.
E. It is likely that some form on specialized nutrition support (TF or TPN) will be necessary.



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A 60 y.o male who is status post a cerebral vascular accident is started on tube feeds at 30 ml per hour via a NGT. The nurse finds that there is a gastric residual of 450 ml four hours after initiating the feedings. The nurse should:

A. Re-feed the gastric residual via the NGT and continue the tube feeds.
B. Discard the gastric residual and continue the tube feeds.
C. Discard the gastric residual and hold the tube feeds as the residual is five times the rate of tube feed infusion.
D. Discard the gastric residual, stop tube feed infusion, and recheck the gastric residual in one hour.
E. Discard the gastric residual, decrease the infusion rate by half, resume feeding and recheck the gastric residual in four hours.

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Regarding the use of enteral formulas in the management of ALI/ARDS

A. Fluid-restricted energy-dense EN formulas may be of use, particularly when the patient is fluid overloaded.
B. A high-fat/low-carbohydrate EN formula designed to decrease CO_2 production is recommended.
C. Full enteral feeding is recommended over trophic feeding during the first week of hospitalization when possible.
D. EN is NOT the preferred method for feeding the ALI/ARDS patient.
E. Answers A, B and C

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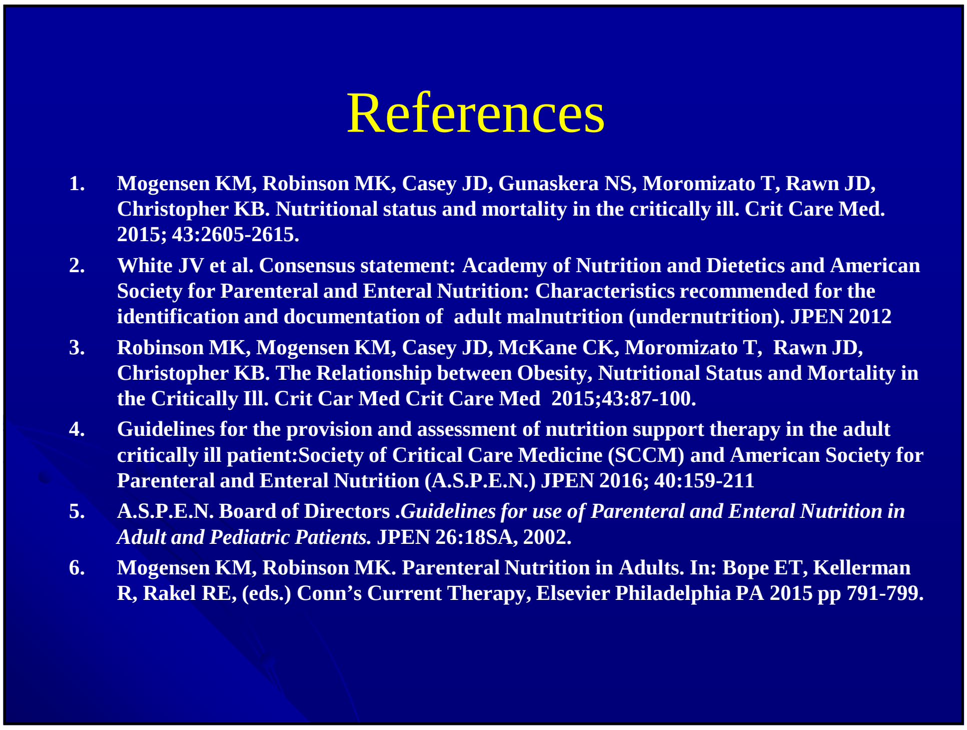


References

1. **Mogensen KM, Robinson MK, Casey JD, Gunaskera NS, Moromizato T, Rawn JD, Christopher KB. Nutritional status and mortality in the critically ill. Crit Care Med. 2015; 43:2605-2615.**
2. **White JV et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN 2012**
3. **Robinson MK, Mogensen KM, Casey JD, McKane CK, Moromizato T, Rawn JD, Christopher KB. The Relationship between Obesity, Nutritional Status and Mortality in the Critically Ill. Crit Car Med Crit Care Med 2015;43:87-100.**
4. **Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient:Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) JPEN 2016; 40:159-211**
5. **A.S.P.E.N. Board of Directors .*Guidelines for use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients.* JPEN 26:18SA, 2002.**
6. **Mogensen KM, Robinson MK. Parenteral Nutrition in Adults. In: Bope ET, Kellerman R, Rakel RE, (eds.) Conn's Current Therapy, Elsevier Philadelphia PA 2015 pp 791-799.**

ICU Prophylaxis

Kathleen J. Haley, MD
Assistant Professor of Medicine, HMS
Associate Physician, BWH

Conflict of Interest

- No conflicts to report

Outline

- DVT
- GI bleeding
- Ventilator-associated events
- Lung Injury
- Delirium
- Early Mobilization

The problem of DVT

- DVT and PE are common in ICU patients
  - 10 - 33% ICU patients in MICU >48hr had DVT on ultrasound study[1,2 ,3]
- DVT and PE have significant attributable morbidity and mortality
  - Asymptomatic proximal DVT carries 13% risk of death at 90d compared to 2% without DVT[4]
  - DVT and PE occur together – approximately 10% patients in ICU with DVT had PE identified[2, 5]
  - PE is not commonly suspected on clinical grounds – > 50% of the PEs detected on autopsy were unexpected[6]

References:
1. DR Hirsch et al. JAMA 1995; vol 274 pp 335-337
2. DJ Cook et al. Crit Care Med 2005; vol 31 pp 48-55
3. PE Marik et al. Chest 1997; vol 111 pp 661-664
4. PT Vaitkus et al., Thromb Haemost 2005; vol 93 pp76-79
5. EH Ibrahim et al., Crit Care Med 2002; vol 30 pp 771-774
6. LA Pineda et al., Chest 2001; vol 120 pp791-795

Risk Stratification

- Balance of harms of venous thromboembolic disease versus harms of prophylactic therapy
- Scoring systems – but none specifically for critically ill patients
  - Caprini[1]
  - Cohen[2]
  - Padua Prediction Score[3]
  - Rogers Score[4]

References:

1. Caprini JA et al. Semin. Hematol. 2001; vol38(2 suppl.5), pp 12 – 19
2. Cohen AT et al. J Thromb Haemost. 2005; vol 94, pp750 – 759
3. Barbar S et al. J Thromb Haemost 2010; vol 8 pp 2450 – 2457
4. Rogers SO et al. J Am Coll Surg 2007; vol 204 pp1211-1221

ICU patients are at-risk for DVT

- Immobilization
- Cancer
  - Hypercoagulable state associated with cancer
  - Therapies also increase risks
- Hypercoagulable state
- Age
- Cardiac failure
- Respiratory failure
- Burns/trauma and recent surgery
- CVA
- Obesity

ICU care imposes additional risks

- Mechanical ventilation/immobilization
- Central venous lines
- Sedation
- Paralytics

Insult to Injury

- DVT pharmacologic prophylaxis either not used, or not used correctly
  - Approximately 70% patients in MICU were on DVT prophylaxis in 16 studies (33 – 100%)
  - When it’s used, it’s frequently disrupted
    - Procedures
    - Bleeding
    - Coagulopathy

Increasing compliance

- Printed guidelines
- Electronic reminders
  - Emails
  - Electronic ordering templates
- Task force/staff education

The good news

- Compliance can be increased
  - Electronic order set templates/prompts
- Increased compliance = Decreased DVTs

Reference: GA Maynard et al. J Hosp Med 2010;5:10 - 18

Regimens (ACCP Guidelines, Ninth edition [1-3])

- Pharmacologic (medical and non-orthopedic surgical patients)
  - Low molecular weight heparin (LMWH)
  - Unfractionated heparin
  - Selective Xa inhibitor: fondaparinux (use in medical patients is off-label)
- Additional pharmacologic approaches for orthopedic surgical patients
  - Direct thrombin inhibitor (dabigatran – off label use)
  - Additional selective Xa inhibitors: apixaban, rivaroxaban
  - Anti-vitamin K agent: warfarin (goal INR 2 – 3)
- Mechanical (all patients)
  - Types: Stockings, compression boots, venous foot pumps
    - Goal is 18h of use every day
  - Problems: Not as effective as pharmacologic prophylaxis, can cause skin ulcerations
  - Benefits: No bleeding
  - Can be added to pharmacologic methods

References:
1. SR Kahn et al., Chest 2012; vol 141 (2 Suppl) pp e195S-226S
2. MK Gould et al., Chest 2012; vol 141 (2Suppl) pp e227s – e277S
3. Y Falck-Ytter et al., Chest 2012;vol 141 (2Suppl) pp e278S – e325S

What about Anti-platelet Agents?

- Very common
- Decreased thrombosis risk compared to placebo
- Two important negatives
  - Less effective than other pharmacologic therapies
  - Increased risk of bleeding

Low molecular weight heparins (LMWH)

- Advantages over unfractionated heparin[1]
  - Once daily dosing
  - Fewer side effects
- Effective
  - Enoxaparin 40 mg SQ daily decreased DVT with side effects similar to placebo (MEDENOX trial)[2]
- Problems
  - More dependent on renal clearance, varies among LMWH
  - Not usually weight based – “capped” doses hard to adjust for obese patients

References:

1. JI Weitz, NEJM 1997; vol 337 pp 688-698
2. MM Samama et al. NEJM; vol 341 pp 793-800

Dalteparin

- Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT)[1]
  - Similar effectiveness as that of enoxaparin – decreased DVT by 55% compared to placebo
  - Adverse events similar to placebo: bleeding in 0.49% dalteparin group, 0.16% placebo
- Examined in patients with renal insufficiency (creatinine clearance < 30 cc/min)[2]
  - No evidence of accumulation with 5,000 IU daily
- Examined in patients >75 yr old[3]
  - Bleeding risk similar to placebo – 1.1% vs 0.7% by d21

References:

1. A Leizorovicz et al., Circulation 2004; vol 110 pp 874-879
2. D Cook et al., Crit Care 2008, vol 12 R32
3. N Kucher et al., Archives of Int Med. 2005; vol 165 pp 341-345

Unfractionated heparin

- Long track record of effectiveness
  - Decreases DVT approximately 60%[1]
- BID or TID
  - TID more effective, but more bleeding[2]
- Doesn't depend on renal clearance
- Complications
  - Heparin-induced thrombocytopenia (HIT) up to 1-2%

References:
1. JF Cade, Crit Care Med 1982; vol 10 pp 448-450
2. CS King et al., Chest 2007; vol 131 pp 507-516

Direct Xa inhibitors

- Examples: Fondaparinux, rivaroxaban, apixaban
  - Can be used in HIT for DVT prophylaxis (off label use)
- Effective – Fondaparinux 2.5 mg SQ daily decreased DVT 46% compared to placebo, same major bleeding as placebo (0.2%) (Arixtra for ThromboEmobolism Prevention in a Medical Indications Study: ARTEMIS trial)[1]
- Problems
  - Renal excretion[2]
  - FDA approved only for post-operative DVT prophylaxis and treatment of PE and DVT

References:
1. AT Cohen et al., BMJ 26 January 2006
2. R Selby and W Geerts, Hematology 2009; pp 286-292

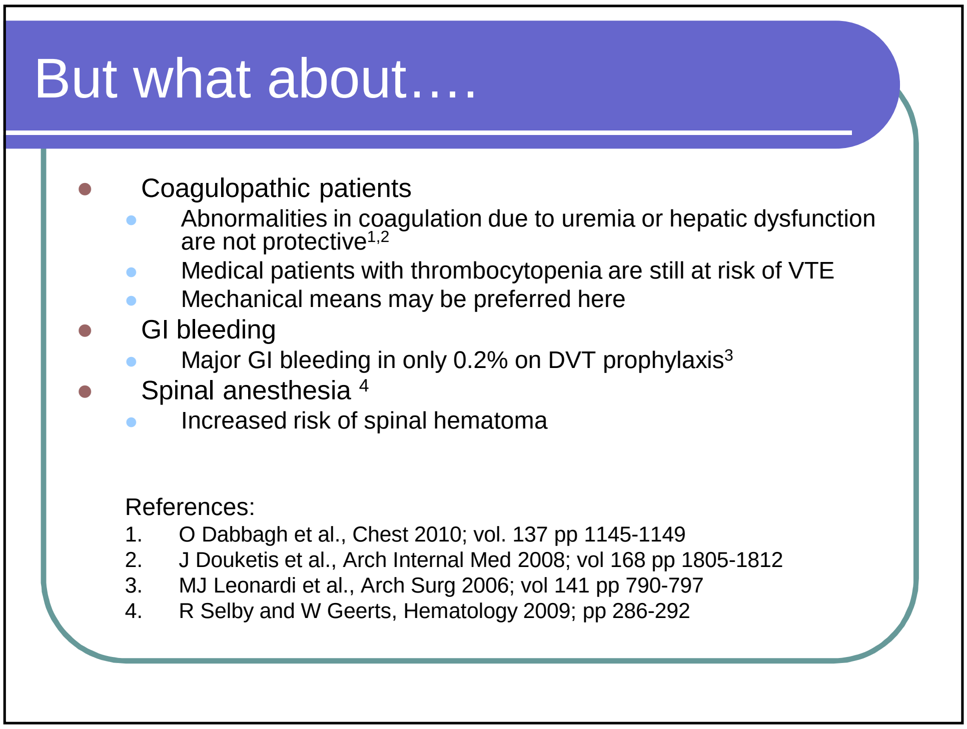
Direct thrombin inhibitors

- Approved for patients with heparin-induced thrombocytopenia (HIT)
- Lepirudin (Hirudin derivative)
  - Available for SC injection – monitor with aPTT
  - Allergic reactions and anaphylaxis
    - Antihirudin in up to 40% treated patients
    - In addition to allergic symptoms, Abs delays clearance
  - Renal excretion
- Argatroban
  - Only IV administration – monitor with aPTT
  - Hepatic clearance
  - Interferes with INR assay
- Oral agents (dabigatran) not FDA approved for this
  - Very limited clinical experience so far

Special considerations

- Renal Insufficiency or failure
  - LMWH is renally cleared, so unfractionated heparin generally preferred for severe renal dysfunction
  - PREVENT[1] and DIRECT[2] studied dalteparin in renal insufficiency
    - Effective in decreasing DVT in critically ill patients with creatinine clearance <30 ml/min (mean 18.9 ml/min in DIRECT)
    - No accumulation of dalteparin as measured by anti-Factor Xa
    - Major bleeding in 7.2%, no association with anti-Factor Xa levels
- Morbid obesity[3]
  - Need weight-based dose adjustments (actual, not ideal)
  - Different proportion lean body to fat
  - If enoxaparin used, a BID schedule is more effective than QD

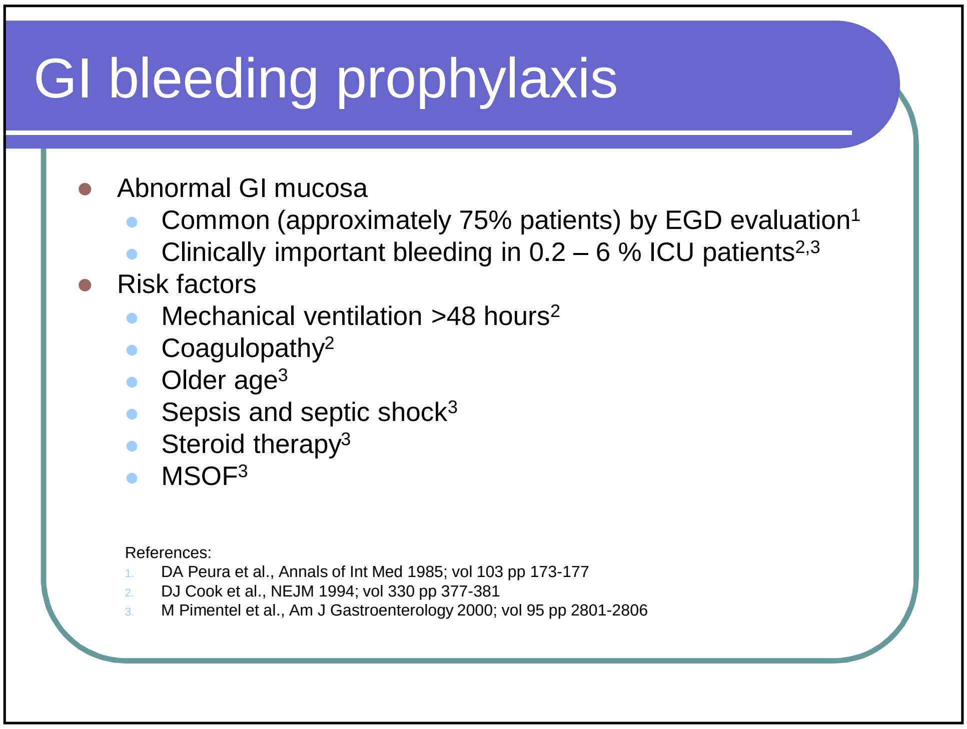
References:
1. D Cook et al., Crit Care 2008; vol 12 R32
2. J Douketis et al., Arch Internal Med 2008 vol 168 pp 1805 – 1812
3. NP Clark Thrombosis Research 2008; vol 123 pp S58 – S61



But what about….

- Coagulopathic patients
  - Abnormalities in coagulation due to uremia or hepatic dysfunction are not protective[1,2]
  - Medical patients with thrombocytopenia are still at risk of VTE
  - Mechanical means may be preferred here
- GI bleeding
  - Major GI bleeding in only 0.2% on DVT prophylaxis[3]
- Spinal anesthesia [4]
  - Increased risk of spinal hematoma

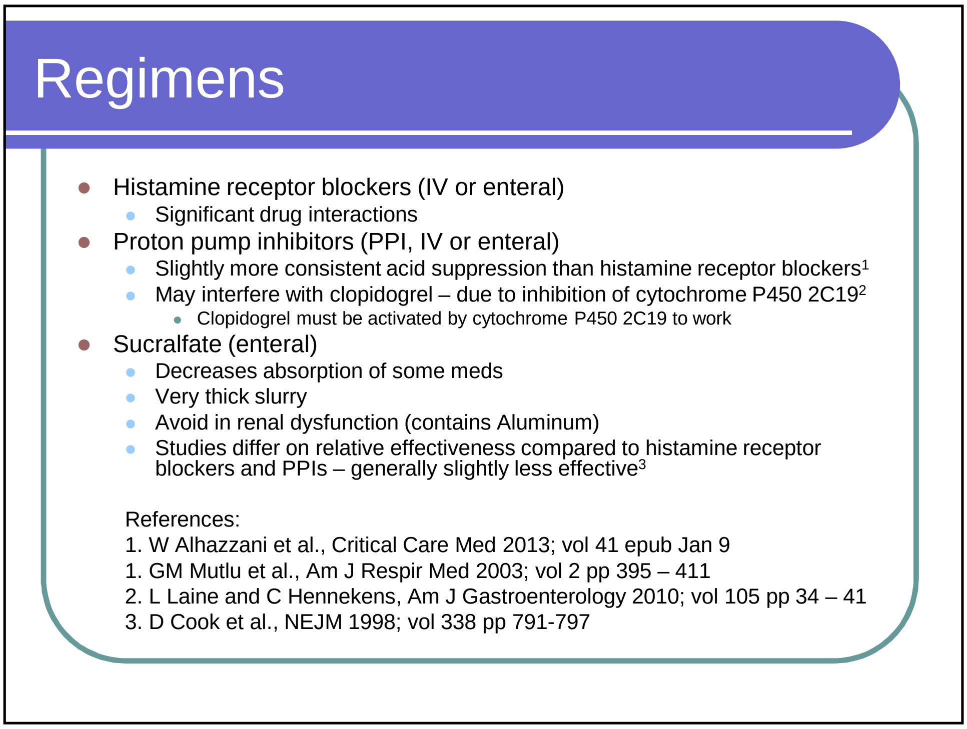
References:
1. O Dabbagh et al., Chest 2010; vol. 137 pp 1145-1149
2. J Douketis et al., Arch Internal Med 2008; vol 168 pp 1805-1812
3. MJ Leonardi et al., Arch Surg 2006; vol 141 pp 790-797
4. R Selby and W Geerts, Hematology 2009; pp 286-292



GI bleeding prophylaxis

- Abnormal GI mucosa
  - Common (approximately 75% patients) by EGD evaluation[1]
  - Clinically important bleeding in 0.2 – 6 % ICU patients[2,3]
- Risk factors
  - Mechanical ventilation >48 hours[2]
  - Coagulopathy[2]
  - Older age[3]
  - Sepsis and septic shock[3]
  - Steroid therapy[3]
  - MSOF[3]

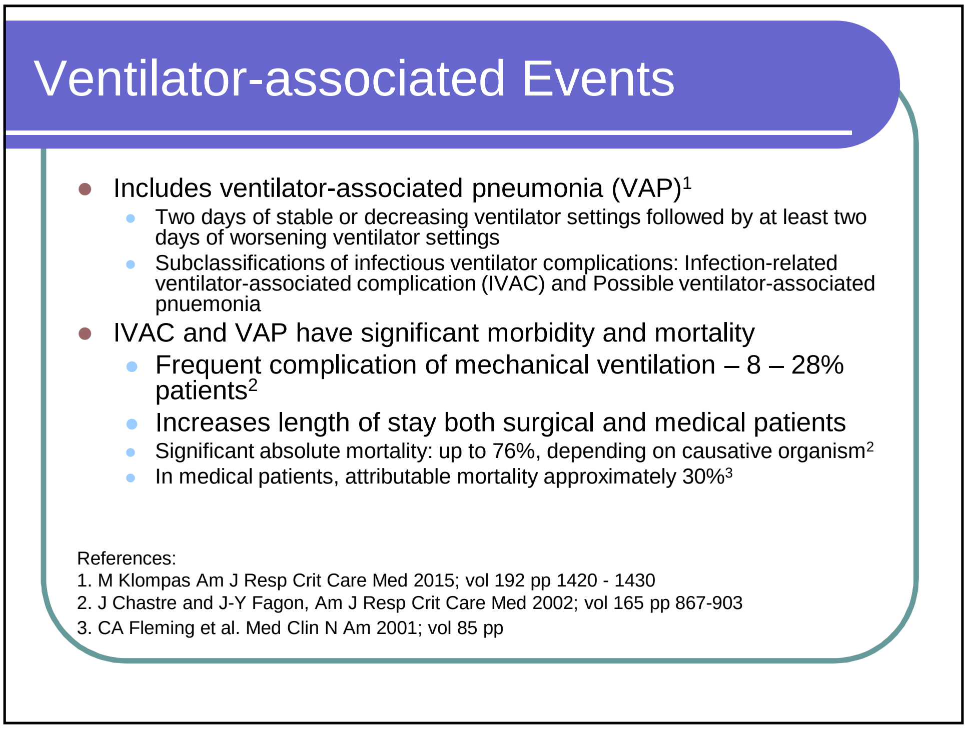
References:
1. DA Peura et al., Annals of Int Med 1985; vol 103 pp 173-177
2. DJ Cook et al., NEJM 1994; vol 330 pp 377-381
3. M Pimentel et al., Am J Gastroenterology 2000; vol 95 pp 2801-2806



Regimens

- Histamine receptor blockers (IV or enteral)
  - Significant drug interactions
- Proton pump inhibitors (PPI, IV or enteral)
  - Slightly more consistent acid suppression than histamine receptor blockers[1]
  - May interfere with clopidogrel – due to inhibition of cytochrome P450 2C19[2]
    - Clopidogrel must be activated by cytochrome P450 2C19 to work
- Sucralfate (enteral)
  - Decreases absorption of some meds
  - Very thick slurry
  - Avoid in renal dysfunction (contains Aluminum)
  - Studies differ on relative effectiveness compared to histamine receptor blockers and PPIs – generally slightly less effective[3]

References:
1. W Alhazzani et al., Critical Care Med 2013; vol 41 epub Jan 9
1. GM Mutlu et al., Am J Respir Med 2003; vol 2 pp 395 – 411
2. L Laine and C Hennekens, Am J Gastroenterology 2010; vol 105 pp 34 – 41
3. D Cook et al., NEJM 1998; vol 338 pp 791-797



Ventilator-associated Events

- Includes ventilator-associated pneumonia (VAP)[1]
  - Two days of stable or decreasing ventilator settings followed by at least two days of worsening ventilator settings
  - Subclassifications of infectious ventilator complications: Infection-related ventilator-associated complication (IVAC) and Possible ventilator-associated pnuemonia
- IVAC and VAP have significant morbidity and mortality
  - Frequent complication of mechanical ventilation – 8 – 28% patients[2]
  - Increases length of stay both surgical and medical patients
  - Significant absolute mortality: up to 76%, depending on causative organism[2]
  - In medical patients, attributable mortality approximately 30%[3]

References:
1. M Klompas Am J Resp Crit Care Med 2015; vol 192 pp 1420 - 1430
2. J Chastre and J-Y Fagon, Am J Resp Crit Care Med 2002; vol 165 pp 867-903
3. CA Fleming et al. Med Clin N Am 2001; vol 85 pp

Preventing IVAC and VAP: ventilator considerations

- Type of suction – closed, in-line best
- Humidifier considerations
  - Heat and moisture exchangers are better than heated humidifiers
  - Heat and moisture exchangers should be changed weekly
    - More frequent changes have higher VAP rates
- Circuit changes
  - Frequency increases costs and doesn't decrease VAP

Reference:
1. P Dodek et al., Annals of Int Med 2004 vol 141 pp305-313

Preventing IVAC and VAP: prevent aspiration

- Effective VAP prophylaxis reduces aspiration of infected secretions
  - Head of bed up
  - Subglottic suctioning can be considered
  - Maintain adequate (20 cm water) cuff pressure
  - Avoid nasotracheal intubation
  - Maintain oral hygiene with chlorohexidine
    - IV Antibiotics for GI tract decontamination controversial
- Rocking beds helpful but expensive
- Early tracheostomy not effective[3]
  - Multicenter study, 600 patients, showed trends for decreased VAP

References:
1. P Dodek et al., Annals of Int Med 2004 vol 141 pp305-313
2. L. Bouadma et al., Crit Care Med 2010 vol 38 PP 789 – 796
3. PP Terragni et al. JAMA 2010 vol 303 pp 1483 - 1489

VAEs requires a mechanical ventilator

- Although "airway protection" frequently invoked for reason to intubate, functional laryngeal reflexes are better at protecting the airway
  - Noninvasive ventilation
  - Early extubation
    - Daily sedation holidays
    - Daily evaluation for readiness to extubate

What about high gastric pH?

- Gastric colonization does increase with PPI and histamine receptor blockers
- Only get IVAC or VAP if aspiration occurs
  - Comparison of sucralfate, PPI and histamine receptor blockers had similar rates of pneumonias[1,2]
  - Can aspirate infected secretions from oropharynx or sinusitis

References:
D Cook et al., NEJM 1998; vol 338 pp 791-797
P-C Lin et al., Crit Care Med 2010; vol 38 pp1197 - 1205

Can We Prevent ARDS?

- "Lung protective" mechanical ventilation is established as treatment strategy in ARDS[1]
- May be effective preventative strategy[2,3]
  - Seen even with short-term ventilation
  - Balance risks of injury with sedation dose

References:

1. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;vol. 342, pp1301-8
2. Fuller BM et al. Crit Care 2013; vol 17, R11
3. Sera Net A et al. JAMA 2012; vol 308, pp 1651-1659

Delirium

- Common problem
- Independent risk factor for death
- Role of prophylaxis unclear
  - Pharmacologic mixed evidence
  - Non-pharmacologic
    - Avoid exacerbating medications
    - Good symptom control
    - Promote normal day/night and sleep cycles
    - Monitor for early signs of delirium

Reference: Z Trogrlic et al. Critical Care 2015; vol. 19: 157

Preventing weakness

- Muscle weakness in critically ill patients[1]
  - Deconditioning: not just immobilization
  - Polyneuropathy and Myopathy of critical illness
  - Medication associated
- Contributes to prolonged mechanical ventilation dependence
- Decreases quality of life, delays recovery
- Independent risk factor for death

Reference:
RD Griffiths et al., Crit Care Med 2010; vol 38 pp779 - 783

Early physical therapy

- Recent studies suggest may preserve strength[1,2,3]
  - Requires multidisciplinary team
  - Feasible
  - Low adverse events
  - Decreased hospital length of stay
  - Better functionality at hospital discharge
- Tantalizing, but more research is needed to confirm the early studies
- Labor-intensive

References:

1. WD Schweickert et al., Lancet 2009 vol 373 pp 1874 – 1882
2. PE Morris et al., Crit Care Med 2008 vol 36 pp 2238-2243
3. DM Needham JAMA 2008 vol 300 PP 1685-1690

Take-Home Points

- Critically ill patients are at increased risk for venous thromboembolic disease (DVT and PE)
- DVT Prophylaxis is effective, but only if it is used
- Histamine receptor blockers or PPIs are effective prophylaxis strategies for preventing stress ulcers
- The common denominator in IVAC and VAP prophylaxis is to avoid aspiration
- Environmental controls can decrease the incidence of delirium
- Exercise is (probably) good for everyone!

Question 1

- You have admitted a 68 yr old man with sepsis due to pneumonia. As part of his routine admission orders, subcutaneous heparin is started for DVT prophylaxis. The patient has required mechanical ventilation and pressor support. Pertinent laboratories include a creatinine of 2.6, INR 2.2, and platelets of 95. What should be done regarding his DVT prophylaxis?

a. The subcutaneous heparin should be discontinued and mechanical DVT prophylaxis started since patient has signs of a coagulopathy

b. The subcutaneous heparin should be continued

c. The subcutaneous heparin should be changed to enoxaparin since the patient has evidence of renal insufficiency

d. The subcutaneous heparin should be discontinued. No DVT prophylaxis is needed since the patient is auto-anticoagulated with an INR of 2.6

e. The subcutaneous heparin should be discontinued and fondaparinux used for DVT prophylaxis

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Question 2

- A 68 yr old woman who has a prior history of upper GI bleeding due to peptic ulcer disease has been admitted to your ICU for urosepsis. The patient requires low-dose norepinephrine to maintain her mean arterial pressure above 65, but her hemodynamics have been improving with IV fluids. She does not require mechanical ventilation. Her PMH is positive for CAD and MI, and she is on aspirin and clopidrogel following coronary artery stent placement. What is true regarding her DVT prophylaxis management?

a. The patient should receive either LMWH or subcutaneous unfractionated heparin for DVT prophylaxis

b. Since she is not on mechanical ventilation, the patient will only require DVT prophylaxis if she requires pressors for more than 48hr.

c. Since she is on two anti-platelet agents, she does not require additional DVT prophylaxis

d. The patient is at higher risk of bleeding due to her history of prior peptic ulcer disease. Unfractionated heparin can be used, as long as there is laboratory monitoring to maintain the aPTT between 1.5 normal value

e. Since she is on two anti-platelet agents and has a history of GI bleeding, she should not receive pharmacologic DVT prophylaxis, but could receive mechanical DVT prophylaxis

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Question 3

- A 55 yr old man with BMI 40 has been admitted to your ICU with multisystem organ failure in the setting of pneumonia. The patient is on mechanical ventilation and pressors, and his creatinine is 1.5. What is correct about his DVT prophylaxis?

a. The risks of DVT and PE are such that full-dose anticoagulation is recommended

b. Either LMWH or unfractionated heparin could be used; for DVT prophylaxis, routine fixed-dosing schedules are effective. Because of their once-daily dosing, LMWH are preferred.

c. Either LMWH or unfractionated heparin could be used with dosing based on ideal body weight

d. Either LMWH or unfractionated heparin could be used with dosing based on actual body weight

e. The increased risk of DVT and PE in the morbidly obese make unfractionated heparin contraindicated – only LMWH dose-adjusted using ideal body weight should be used

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Question 4

- A 62 yr old man with a COPD exacerbation due to pneumonia has been admitted to your ICU. He requires mechanical ventilation. He has been receiving DVT prophylaxis with unfractionated heparin. Last night, he had a 2 hour episode of hypotension following a turn. During that episode, his oxygen requirements increased, but he subsequently has tolerated tapering his FiO2 back to 50%. Which of the following is true?

a. Since he has been on DVT prophylaxis, his risk of DVT or PE is extremely low, and does not need to be considered as a cause of his overnight symptoms

b. Since he has been on DVT prophylaxis with unfractionated heparin instead of LMWH, he is at moderate risk for DVT or PE

c. Although he has been on adequate DVT prophylaxis, he remains at risk, since approximately 10% of patients with prophylaxis develop DVT and 10% of those patients develop PE

d. Since his symptoms have resolved, his risk of DVT/PE is low. Patients on mechanical ventilation have poor tolerance for any further decrement in respiratory function, therefore PE is usually suspected on clinical grounds

e. Although he has received DVT prophylaxis, his risk of DVT/PE remains high. He should be started on full-dose anticoagulation until PE is ruled out.

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Question 5

- A 45 yr old man with respiratory failure due to pulmonary edema in the setting of cardiomyopathy and renal failure has just been admitted to your ICU. On admission, he is on norepinephrine to maintain his BP. He was intubated in the ED. Which of the following could decrease his risk of ventilator-associated pneumonia?

a. Keep the head of the bed elevated, use in-line suctioning apparatus changed every 2days, add IV antibiotics for GI tract decontamination

b. Keep the head of the bed elevated, change the humidifier circuit every week, proceed to tracheostomy if the patient requires ventilator support for more than 7d

c. Use subglottic suctioning, add IV antibiotics for GI tract decontamination, use in-line suctioning changed daily

d. Use subglottic suctioning, keep the head of the bed elevated, maintain oral hygeine with chlorhexidine rinses/swabs

e. Keep the head of the bed elevated, proceed to early tracheostomy if the patient requires ventilator support for more than 7d, use oral topical (polymixin B) and IV antibiotics for GI tract decontamination

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Bibliography

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- W Geerts and R Selby. Prevention of venous throboembolism in the ICU. Chest 2003; vol 124: 357S-363S
- J Chastre and J-Y Fagon. Ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002; vol 165: 867 - 903
- PP Terragni et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. JAMA 2010 vol 303: 1483-1489
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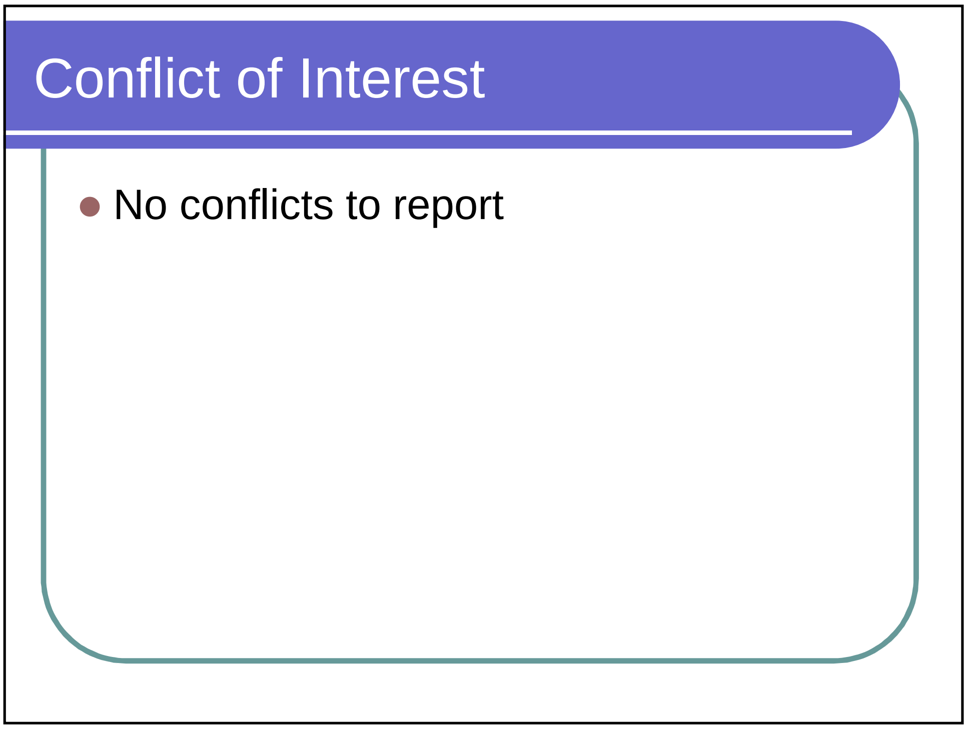

Conflict of Interest

- No conflicts to report

BRIGHAM AND
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Treatment of the Patient with Burns and Inhalational Injuries

Simon G Talbot, MD
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Boston, MA, USA

Disclaimer

- I have no proprietary or financial interest in any of the disorders, products, or devices mentioned

Overview

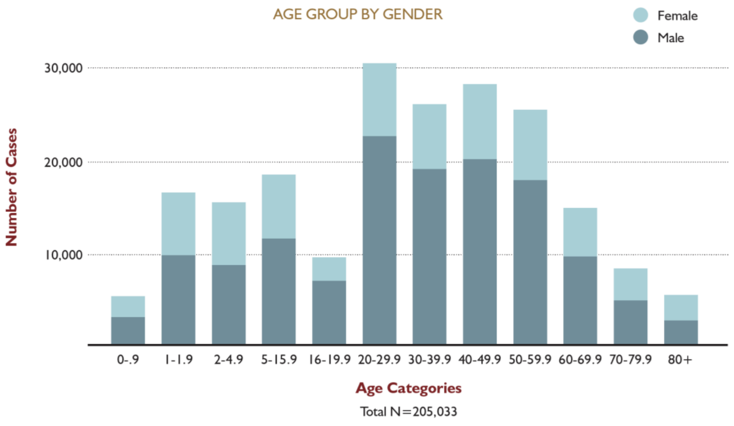
- Epidemiology
- Initial assessment
  - ABCs, secondary survey
  - Escharotomies
  - When to transfer
  - Area of burn (Rule of 9s)
  - Depth of burn
  - Dressings
  - Inhalational injuries
  - CO poisoning
- Resuscitation
  - Parkland protocol
- Surgical management
  - Early excision and grafting
  - Allograft and xenograft
  - Cultured epidermal autograft
  - Flaps
  - Dressings
  - Complications
- Special cases
  - Electrical burns
- ICU management
  - Nutrition

Epidemiology

- Annual incidence (USA)
  - 486000 burn injuries receiving treatment
  - 3275 fire and burn deaths
  - 40000 hospital admission (30000 to Burn Centers)
- Burn Center Admissions
  - Survival 2006-2015: 96.7%
  - Gender: 68% male
  - Ethnicity: 58% Caucasian, 21% African-American, 13% Hispanic
  - Cause: 41% flame/fire, 33% scald, 9% contact, 3% chemical, 3% electrical
  - Location: 68% home, 10% occupational, 7% street
  - 10 year improvements: LOS 1 days less, mortality down from 4% to 3%

Source: www.ameriburn.org and ABA National Burn Repository (2016 report)

Epidemiology



Total N=205,033

Source: ABA National Burn Repository (2016 report)

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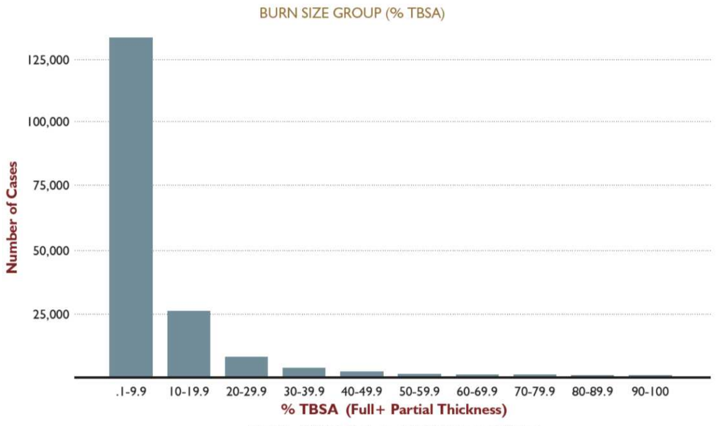
Epidemiology



Total N=177,498 (Excluding 27,535 Unknown/Missing)

Source: ABA National Burn Repository (2016 report)

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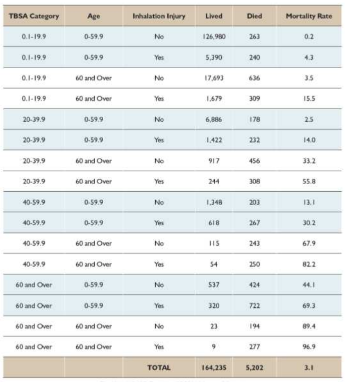
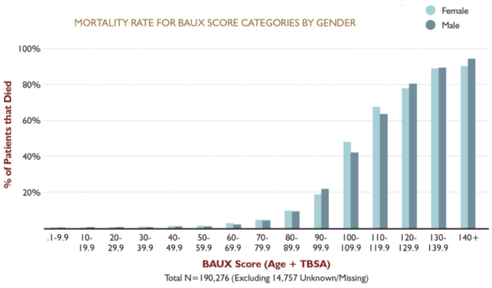
Mortality

- Death proportional to:
  - Advancing age, burn size, inhalation injury (increase 20x)
- Hospital stay = 1 day per percent TBSA



TBSA Category	Age	Inhalation Injury	Lived	Died	Mortality Rate
0.1-19.9	0-59.9	No	126,980	263	0.2
0.1-19.9	0-59.9	Yes	5,390	240	4.3
0.1-19.9	60 and Over	No	17,693	636	3.5
0.1-19.9	60 and Over	Yes	1,679	309	15.5
20-39.9	0-59.9	No	6,886	178	2.5
20-39.9	0-59.9	Yes	1,422	232	14.0
20-39.9	60 and Over	No	917	456	33.2
20-39.9	60 and Over	Yes	244	308	55.8
40-59.9	0-59.9	No	1,348	203	13.1
40-59.9	0-59.9	Yes	618	267	30.2
40-59.9	60 and Over	No	115	243	67.9
40-59.9	60 and Over	Yes	54	250	82.2
60 and Over	0-59.9	No	537	424	44.1
60 and Over	0-59.9	Yes	320	722	69.3
60 and Over	60 and Over	No	23	194	89.4
60 and Over	60 and Over	Yes	9	277	96.9
		TOTAL	**164,235**	**5,202**	**3.1**

Total N=169,437 (Excluding 35,596 Unknown/Missing)


MORTALITY RATE FOR BAUX SCORE CATEGORIES BY GENDER

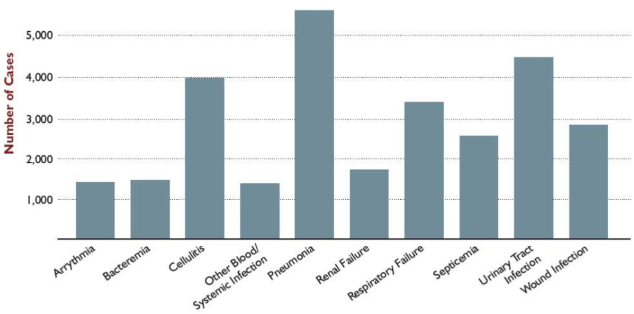
Total N=190,276 (Excluding 14,757 Unknown/Missing)

Source: ABA National Burn Repository (2016 report)

Complications

- Complications
  - Pneumonia (5.4% of flame burns) – especially with ventilation >4 days

COMPLICATIONS: FREQUENCY OF TOP TEN CLINICALLY RELEVANT COMPLICATIONS

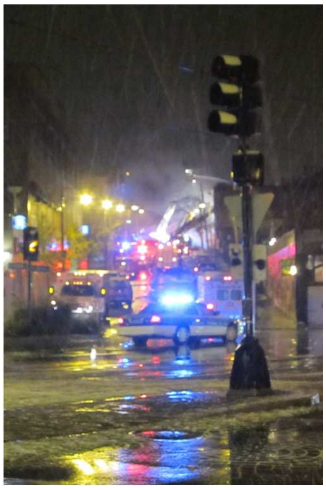


Total N=200,867 (Excluding 4,166 cases from non ABA burn registry software centers)

Source: ABA National Burn Repository (2016 report)

Initial assessment - 1

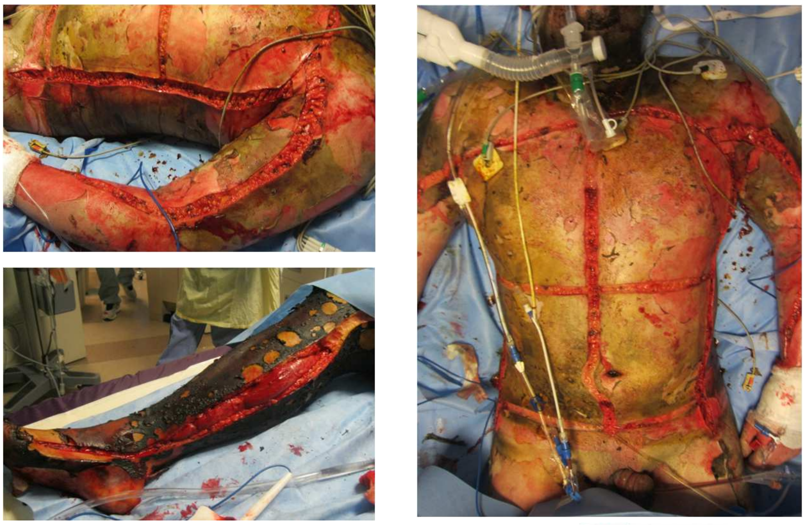
- Definition
  - A burn is the partial or complete destruction of skin caused by some form of energy, usually thermal energy
- Burns are frequently associated with trauma
  - Start by ignoring the burn
- Proceed with routine trauma assessment
  - Primary survey
    - ABC
  - Secondary survey
    - Head to toe examination
    - C-spine
  - Tertiary survey in the future



Initial assessment - 2

- Airway
  - 100% FiO2
  - Signs of inhalation
    - Decreased MS, stridor, carbonaceous sputum, high CO
  - When in doubt, intubate
- Breathing
  - CXR
- Circulation
  - Access (non-burned skin vs CVL)
  - Escharotomies (circumferential burns)
    - Limb and/or chest
    - Can be done bedside – cautery reduces bleeding
    - Medial and lateral on limbs (avoid major nerves)
    - May also need fasciotomies (pressure 25-40mmHg)
  - EKG
- Disability

Escharotomies



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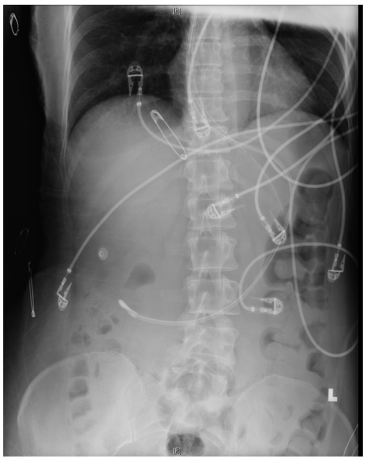
Initial assessment - 3

- Exposure
  - Calculate TBSA
  - Keep the room HOT
  - Warmed IVF
  - Blankets and Bair Hugger
- Fluids
  - >20% TBSA initiate resuscitation
  - Foley
- Routine labs and toxicology screen
- NGT (+/- small bore feeding tube post-pyloric)
- Pain control
- Dressings
- Tetanus booster (or immune globulin)
- Ocular involvement (specialist referral)



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Burn Center referral criteria

1. Partial thickness burns greater than 10% TBSA
2. Burns that involve the face, hands, feet, genitalia, perineum, or major joints
3. Third degree burns in any age group
4. Electrical burns, including lightning
5. Chemical burns
6. Inhalation injury
7. Pre-existing medical disorders
8. Concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality (stabilize first)
9. Children
10. Patients who will require special social, emotional, or rehabilitative intervention

Source: www.ameriburn.org.
Advanced Burn Life Support

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TEACHING AFFILIATE

Prior to transfer

- Airway stabilized
- IV access established
- Estimated TBSA
- Parkland initiated
- Pain control
- Dry sterile dressings to burns

Source: www.ameriburn.org.
Advanced Burn Life Support

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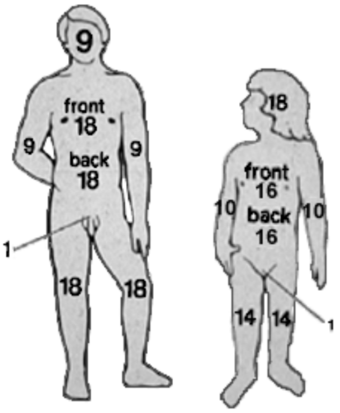
Area of burn

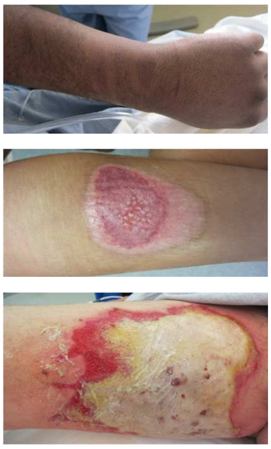
- Rule of 9s
- Do not count first degree burns
- Note: Children’s heads comprise greater % TBSA
- Palm = 1%



Source: www.ameriburn.org.
Advanced Burn Life Support

Depth of burn

- **First Degree** (*Partial Thickness*)
  - Superficial, red, sometimes painful
  - Damage to epidermis
- **Second Degree** (*Partial Thickness*)
  - Skin may be red, blistered, swollen, very painful
  - Damage to dermis
  - Skin adnexa remain
  - Heal by re-epithelialization from adnexa
  - Deep second are more like third degree
- **Third Degree** (*Full Thickness*)
  - Whitish, charred or translucent, no pin prick sensation in burned area
  - Full thickness of skin damaged
  - Heal from the skin edges (and will lead to scarring unless small)
  - Typically need excision
- **Fourth Degree**
  - Involves muscle, tendon, bone

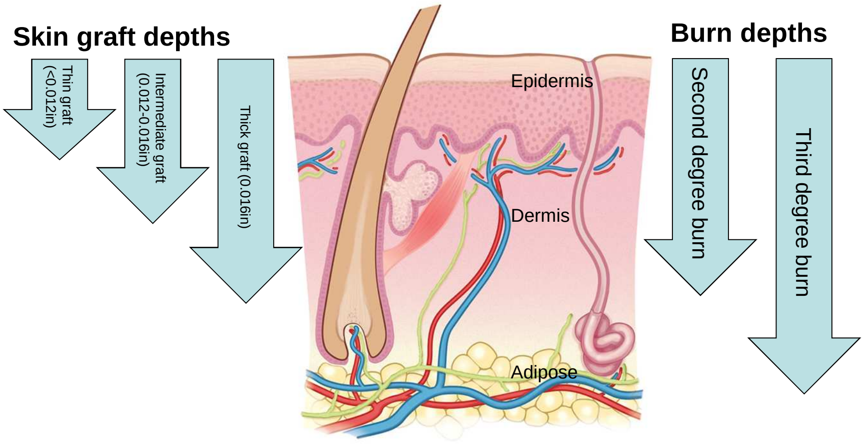


Source: www.ameriburn.org.
Advanced Burn Life Support

Thickness of burns and grafts

Skin graft depths

Burn depths


Thin graft (<0.012in)
Intermediate graft (0.012-0.016in)
Thick graft (0.016in)
Epidermis
Dermis
Adipose
Second degree burn
Third degree burn

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING AFFILIATE

Dressings

- Prophylactic systemic antibiotics do not improve outcomes and cause drug resistance
- Topical treatment (commonly silver) are effective at preventing and treating systemic infection
- First degree burns
  - Minimal dressings
  - Moisturizer eg Vitamin A&D
- Second degree
  - Debride large blisters and loose skin
  - Bacitracin and petroleum gauze eg Xeroform
  - Skin substitutes eg Transcyte®, Biobrane®
- Third degree
  - Larger areas will need operative excision
  - Silver sulfadiazine
    - Watch for leukopenia
  - Silver nitrate
    - Watch for metabolic acidosis
  - Mafenide
    - Penetrates cartilage
    - Watch for methemoglobinemia
  - Other nanocrystalline dressings
    - Acticoat™, AquacelAg™, MepilexAg™

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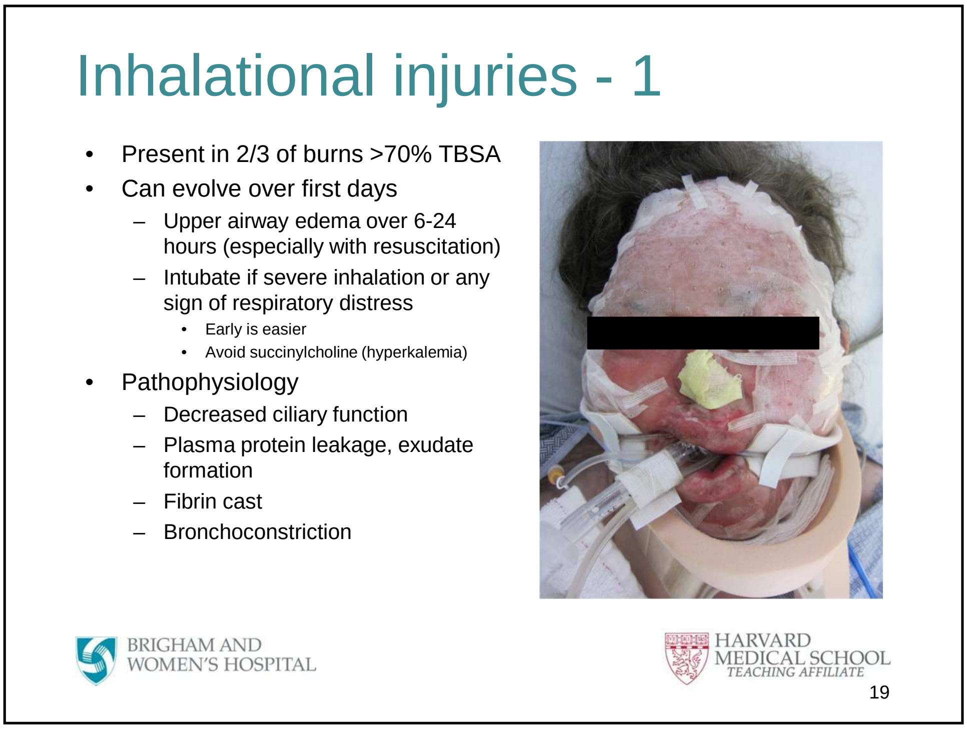
HARVARD MEDICAL SCHOOL TEACHING AFFILIATE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Inhalational injuries - 1

- Present in 2/3 of burns >70% TBSA
- Can evolve over first days
  - Upper airway edema over 6-24 hours (especially with resuscitation)
  - Intubate if severe inhalation or any sign of respiratory distress
    - Early is easier
    - Avoid succinylcholine (hyperkalemia)
- Pathophysiology
  - Decreased ciliary function
  - Plasma protein leakage, exudate formation
  - Fibrin cast
  - Bronchoconstriction

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HARVARD MEDICAL SCHOOL
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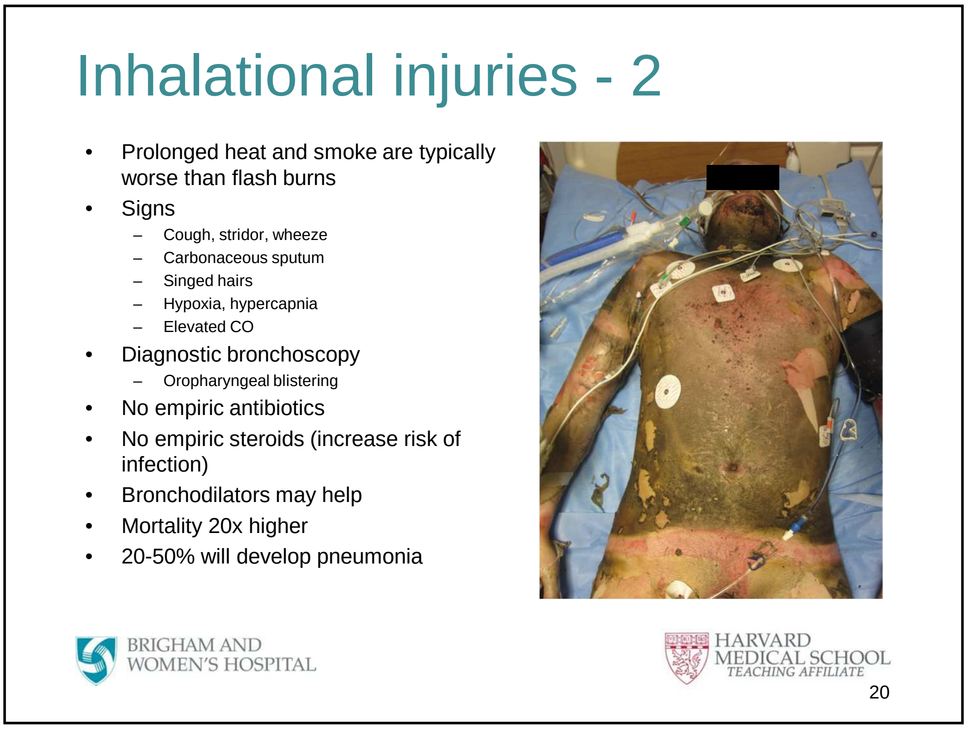
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Inhalational injuries - 2

- Prolonged heat and smoke are typically worse than flash burns
- Signs
  - Cough, stridor, wheeze
  - Carbonaceous sputum
  - Singed hairs
  - Hypoxia, hypercapnia
  - Elevated CO
- Diagnostic bronchoscopy
  - Oropharyngeal blistering
- No empiric antibiotics
- No empiric steroids (increase risk of infection)
- Bronchodilators may help
- Mortality 20x higher
- 20-50% will develop pneumonia

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL
TEACHING AFFILIATE

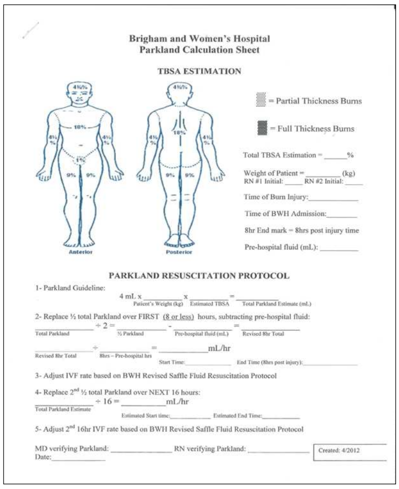
CO poisoning

- Beware of CO poisoning
  - Always obtain a CO level in moderate-severe burns
  - O2 saturation will be normal
- Half-life 4h on room air, 1h on 100% O2
- No cyanosis
- Levels
  - 15-20% confusion
  - 20-40% disorientation
  - 40+% coma
- Treat with 100% FiO2
  - Hyperbaric treatment controversial (usually detracts from more important management)
- Consider cyanide poisoning if unexplained lactic acidosis and cardiac depression
  - Treat with hydroxocobalamin (Cyanokit^{TM})

www.rsikit.com

Resuscitation - 1

- Parkland formula
  - Most common (there are others)
  - Lactated ringers
  - Formula
    - 4 x weight (kg) x %TBSA
      - Give 1/2 in the first 8 hrs
      - Give other 1/2 in next 16 hrs
  - Caveats
    - Tends to over-resuscitate causing 'fluid creep'
    - Adjust based on urine output (goal >0.5mL/h)
    - May supplement albumin (literature varies)
    - Vitamin C may help reduce fluid volume
    - Delay in starting associated with mortality


4½%
18%
4½%
4½%
1%
9%
9%
Anterior
4½%
18%
4½%
4½%
9%
9%
Posterior

Brigham and Women's Hospital
Parkland Calculation Sheet

TBSA ESTIMATION

▨ = Partial Thickness Burns

■ = Full Thickness Burns

Total TBSA Estimation = _____%

Weight of Patient = _________(kg)
RN #1 Initial: _____ RN #2 Initial: _____

Time of Burn Injury:____________

Time of BWH Admission:________

8hr End mark = 8hrs post injury time

Pre-hospital fluid (mL): _________

PARKLAND RESUSCITATION PROTOCOL

1- Parkland Guideline:
4 mL x _________ x _________ = _________
Patient's Weight (kg) Estimated TBSA Total Parkland Estimate (mL)

2- Replace ½ total Parkland over FIRST (8 or less) hours, subtracting pre-hospital fluid:
_________ ÷ 2 = _________ - _________ = _________
Total Parkland ½ Parkland Pre-hospital fluid (mL) Revised 8hr Total

_________ ÷ _________ = _________mL/hr
Revised 8hr Total 8hrs – Pre-hospital hrs
Start Time:__________ End Time (8hrs post injury):____________

3- Adjust IVF rate based on BWH Revised Saffle Fluid Resuscitation Protocol

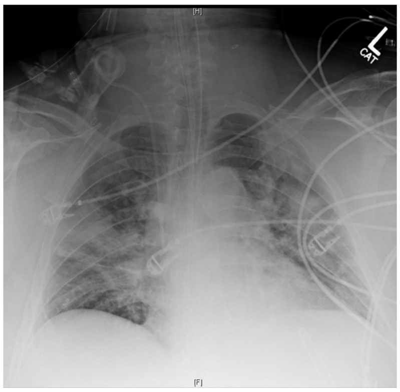
4- Replace 2nd ½ total Parkland over NEXT 16 hours:
_________ ÷ 16 = _________mL/hr
Total Parkland Estimate
Estimated Start time:__________ Estimated End Time:__________

5- Adjust 2nd 16hr IVF rate based on BWH Revised Saffle Fluid Resuscitation Protocol

MD verifying Parkland: ____________ RN verifying Parkland: ____________ Created: 4/2012
Date:____________

Resuscitation - 2

- Over-resuscitation may be associated with:
  - Compartment syndrome
    - Extremity
    - Abdominal (watch bladder pressures)
  - Third spacing
  - Poor vascular supply to burn
  - Pulmonary complications



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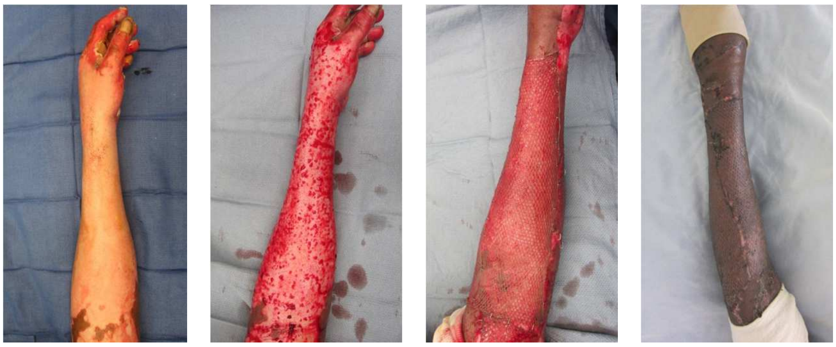
HARVARD MEDICAL SCHOOL *TEACHING AFFILIATE*

Goals of burn surgery



Burned tissue → Prepare the bed → Cover the wound → Healing

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HARVARD MEDICAL SCHOOL *TEACHING AFFILIATE*

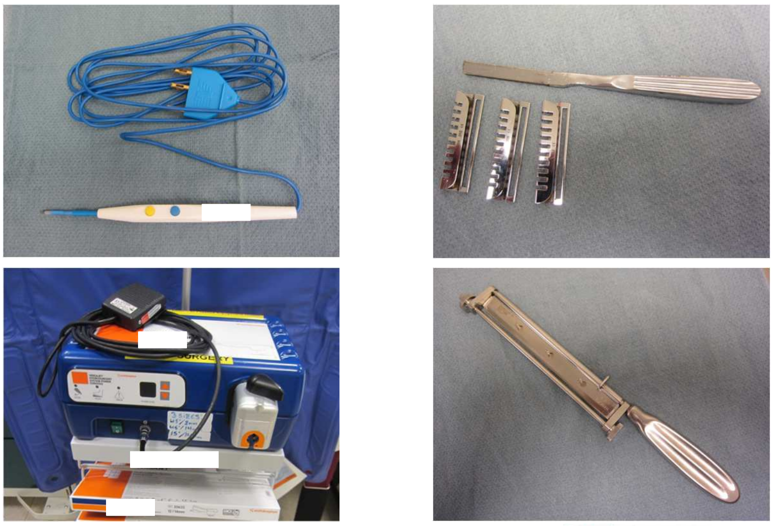
Early excision and grafting

- First and superficial second degree burns should heal with dressings alone
  - Scarring dependent on:
    - Individual patient factors
    - Time to healing (>2-3 weeks)
    - Wound/incision location
- Deeper second degree and third degree burns typically require excision
  - Early excision (24-72 hrs) is associated with improved outcomes
  - Begins when patient is stable
  - Excision and grafting
  - Excision and closure

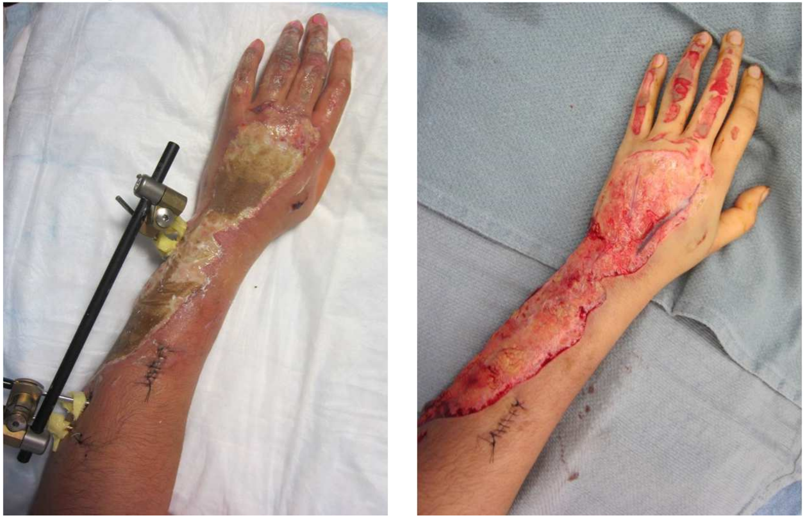
Preparing the stage

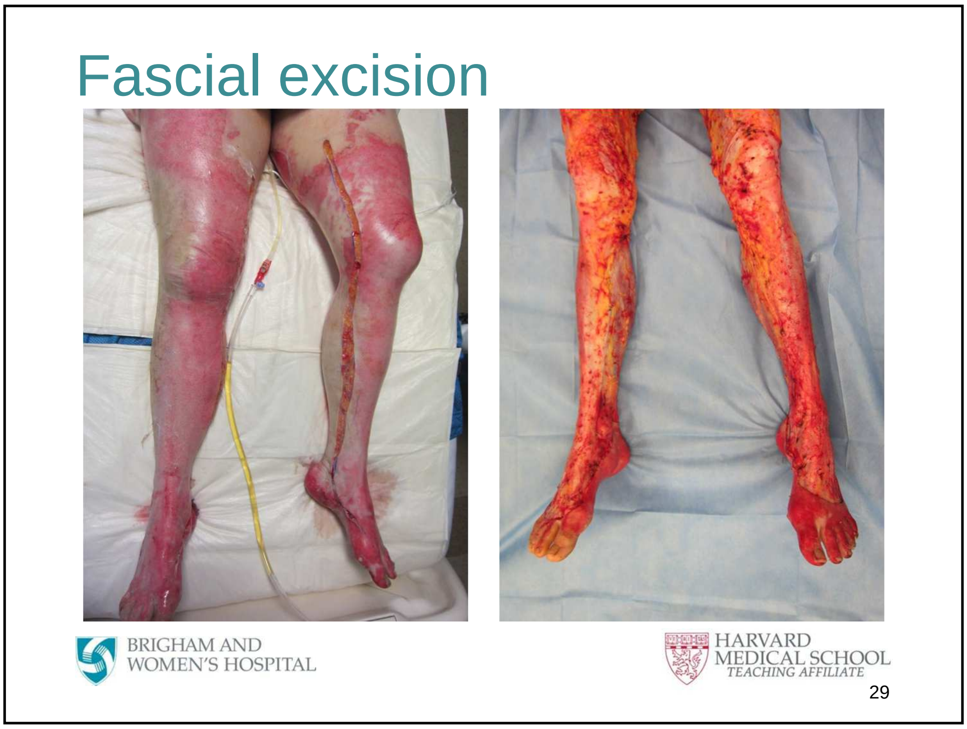
- Excision
  - Tangential
    - Leaves fat
    - Less vascular
    - Requires more 'judgement'
    - Equipment
      - Versajet™
      - Weck knife
      - Watson blades
  - Fascial
    - Simple
    - Highly vascular bed
    - Equipment
      - Monopolar cautery
- Goals
  - Remove all infection
  - Remove all debris
  - Eliminate shear
  - Prevent fluid (blood, serum) collecting
  - Maximize vascularity of the bed

How do we do it?



Tangential excision





Fascial excision

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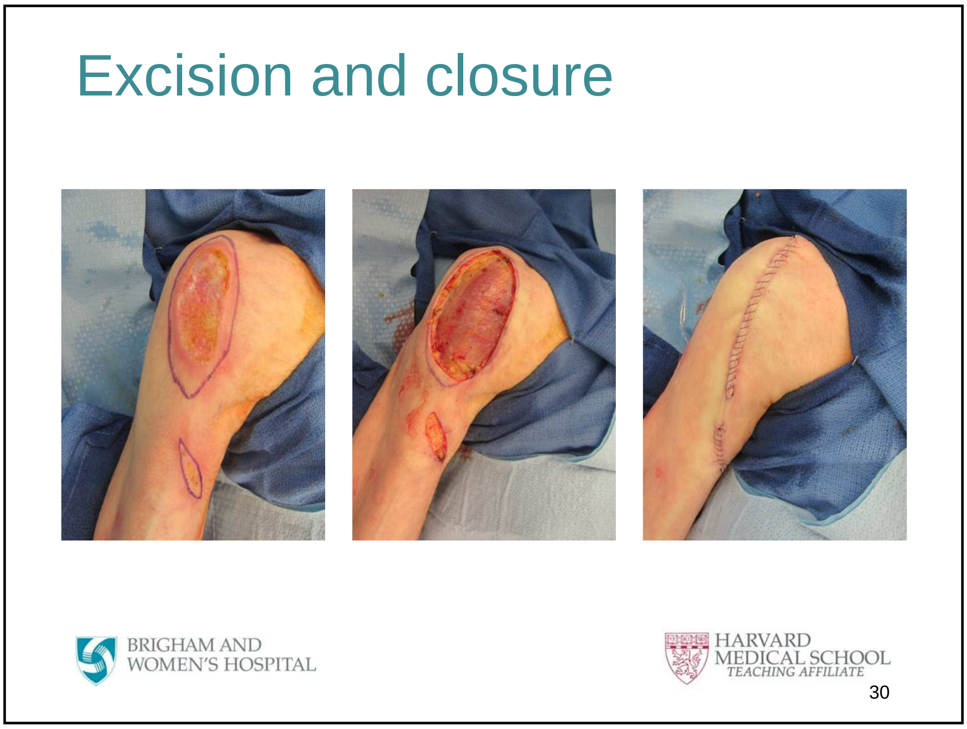

Excision and closure

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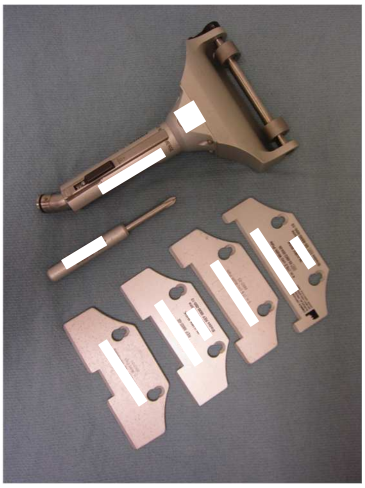
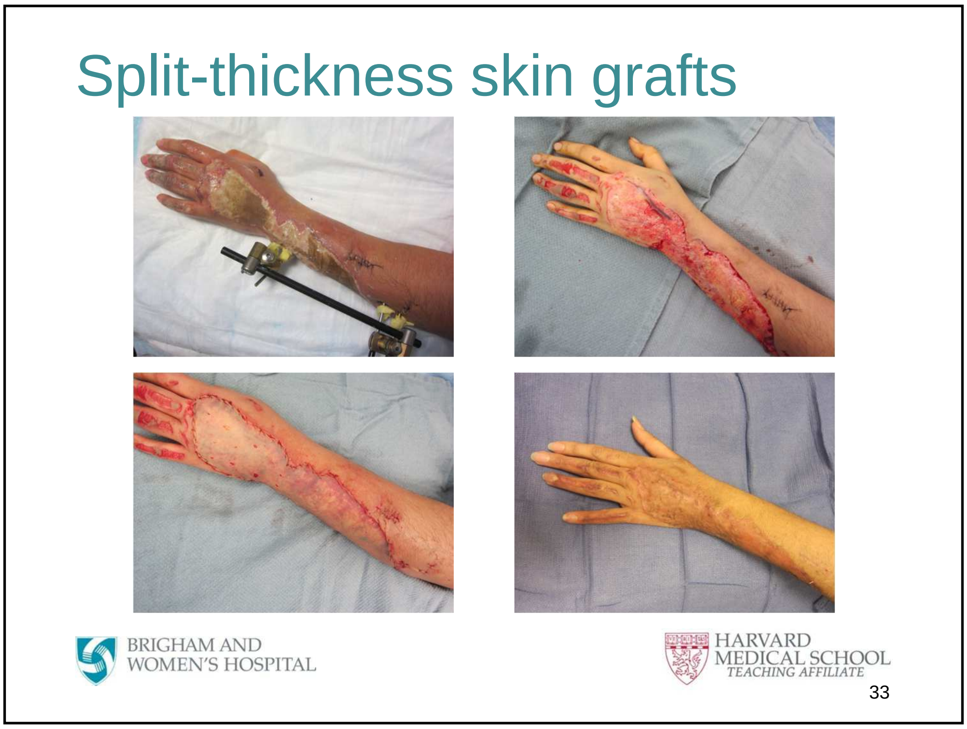
Skin graft basics

- ‘Skin graft’
  - surgical procedure by which skin is placed over a wound to permanently replace damaged or missing skin
- Skin grafts heal by:
  - Serum imbibition (24 hours) – diffusion
  - Inosculation (up till day 5) – neovascularization
  - Revascularization

Split-thickness skin grafts



- Advantages
  - Availability of donor sites
  - Better ‘take’
- Disadvantages
  - More contraction and contractures
  - Less durable
  - Poorer cosmesis (color and texture)
  - Larger donor site scars



Split-thickness skin grafts

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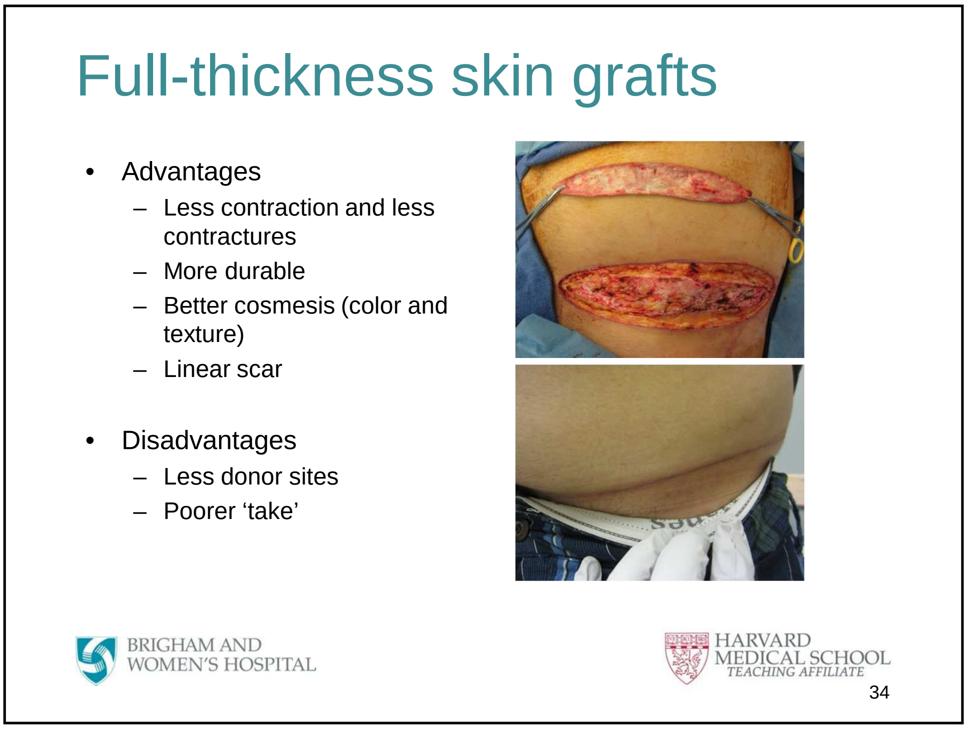

Full-thickness skin grafts

- Advantages
  - Less contraction and less contractures
  - More durable
  - Better cosmesis (color and texture)
  - Linear scar
- Disadvantages
  - Less donor sites
  - Poorer 'take'

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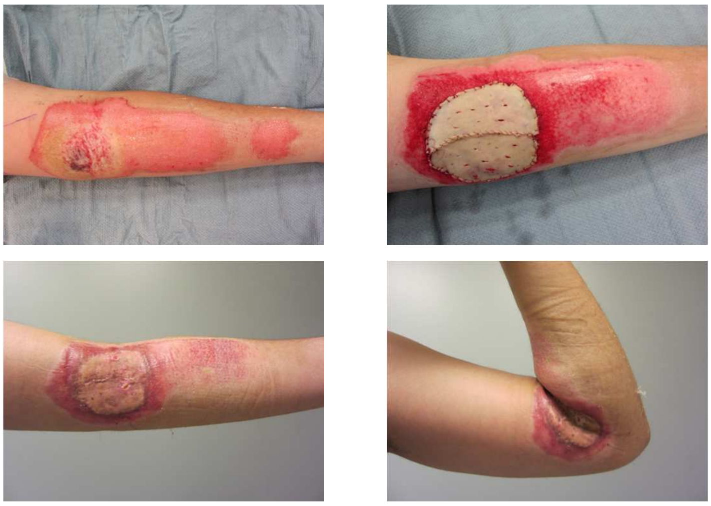
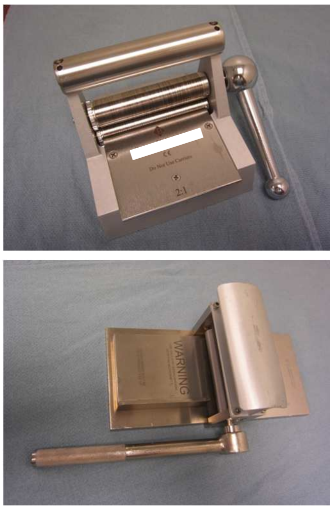
Full-thickness skin grafts

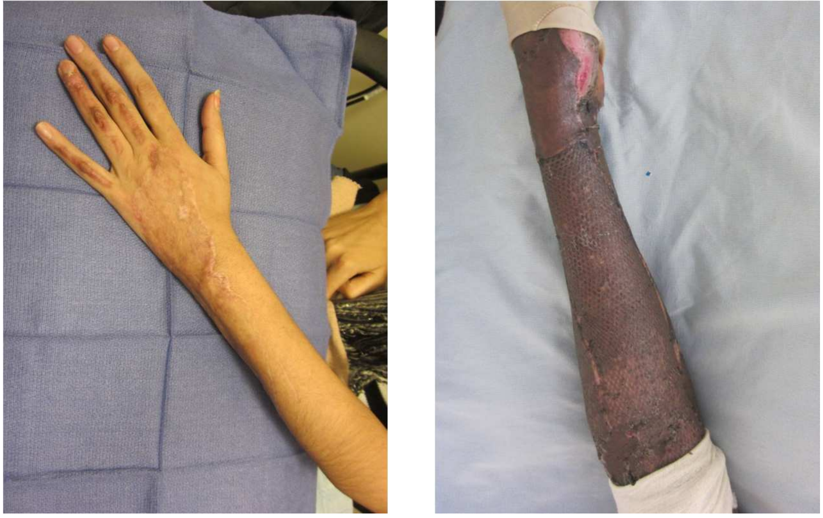


Meshed vs sheet grafts

- Meshed
  - Lets less skin 'go further'
  - Allows egress of fluid beneath graft
  - Allows conformation to irregular shapes
  - Can have a 'reptilian' appearance
  - Increased contraction (secondary healing)
  - Types 1:1, 1:1.5, 1:2, 1:3, 1:6
- Sheet
  - Less contraction (eg hands)
  - Better cosmesis (eg face)
  - Uses more skin for less coverage
  - Harder to conform to irregularities
  - Can fail due to fluid beneath graft
  - Often 'pie crust'



Meshed vs sheet grafts



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Thickness of a STSG

- The thicker it gets, the more it behaves like a FTSG

- Thin (eg 0.008-0.012 in)
  - Useful in tenuous vascularity (eg Integra)
  - Useful in repeatedly harvested sites (less robust dermis)
  - Useful when planning to re-harvest (heals quicker)
  - May be all that is available (eg elderly)
- Intermediate (eg 0.012-0.016 in)
- Thick (eg 0.016-0.020 in)
  - Useful where contracture is a problem eg neck, hands, face
- Very thick (eg >0.020 in)
  - Unique locations eg glabrous/palmar skin

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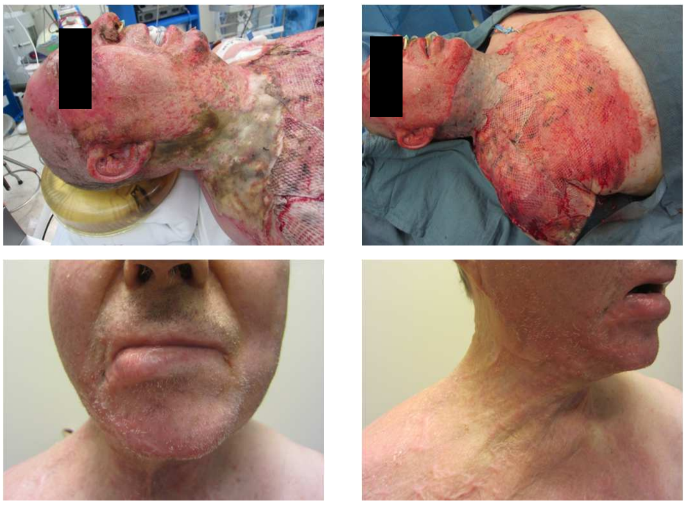
Thickness of a STSG



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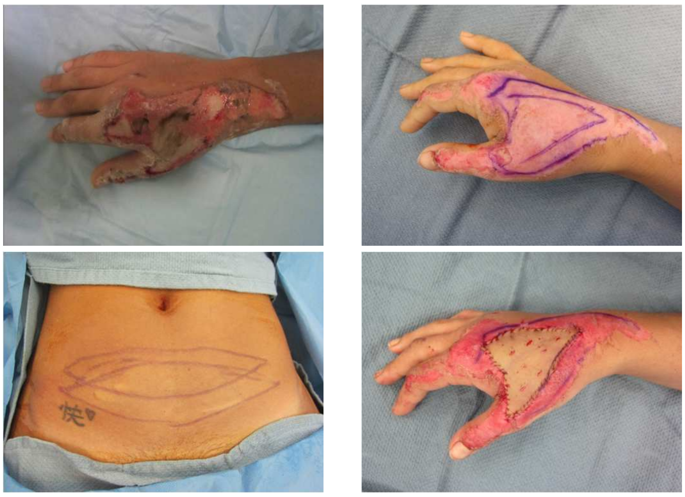
[redacted]

Caveats with recipient sites

- Face
  - Sheet grafts
  - Donor sites with similar skin eg retroauricular, supraclavicular, medial arm
- Hands
  - Sheet grafts
  - Contractures a major problem
  - Splinting including k-wires
  - Don't forget finger nails
- Joints
  - Minimize contracture
  - Splinting to reduce shear

Hands



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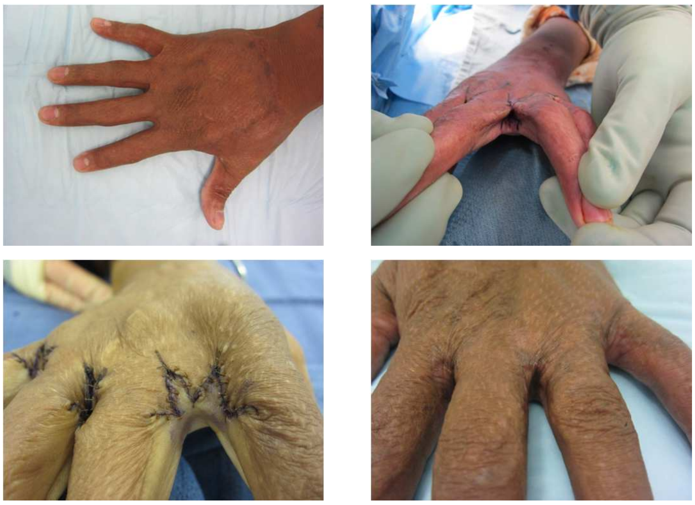
More hands



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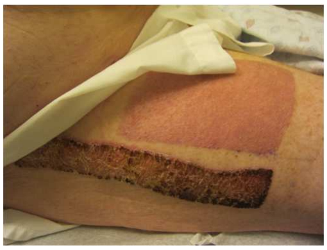
Skin graft donor sites

- Split-thickness sites
  - Upper thigh
  - Buttocks
  - Scalp
  - Anywhere unburned
- Full-thickness sites
  - Retroauricular
  - Medial arm
  - Supraclavicular
  - Abdomen (tummy tuck)
  - Inguinal crease
  - Adjacent to other scars



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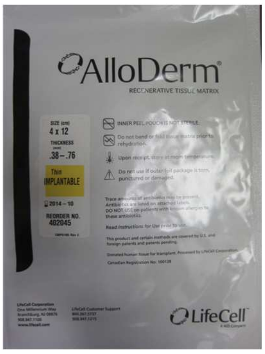
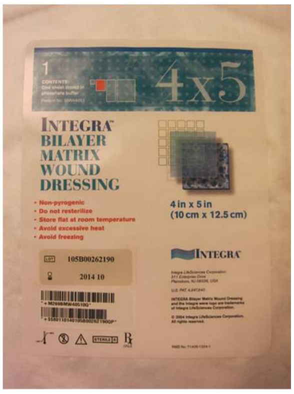
Adjuncts to skin grafting

- Dermal regeneration template
- Acellular dermal matrix


AlloDerm
REGENERATIVE TISSUE MATRIX
LifeCell


4x5
INTEGRA BILAYER MATRIX WOUND DRESSING
4 in x 5 in
(10 cm x 12.5 cm)
INTEGRA

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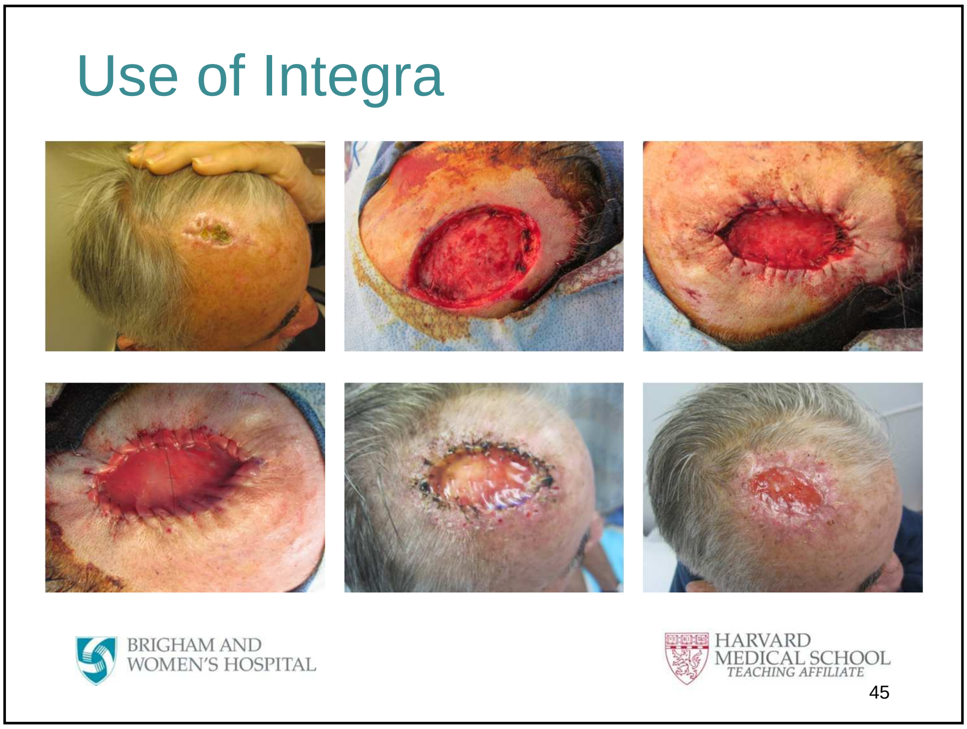
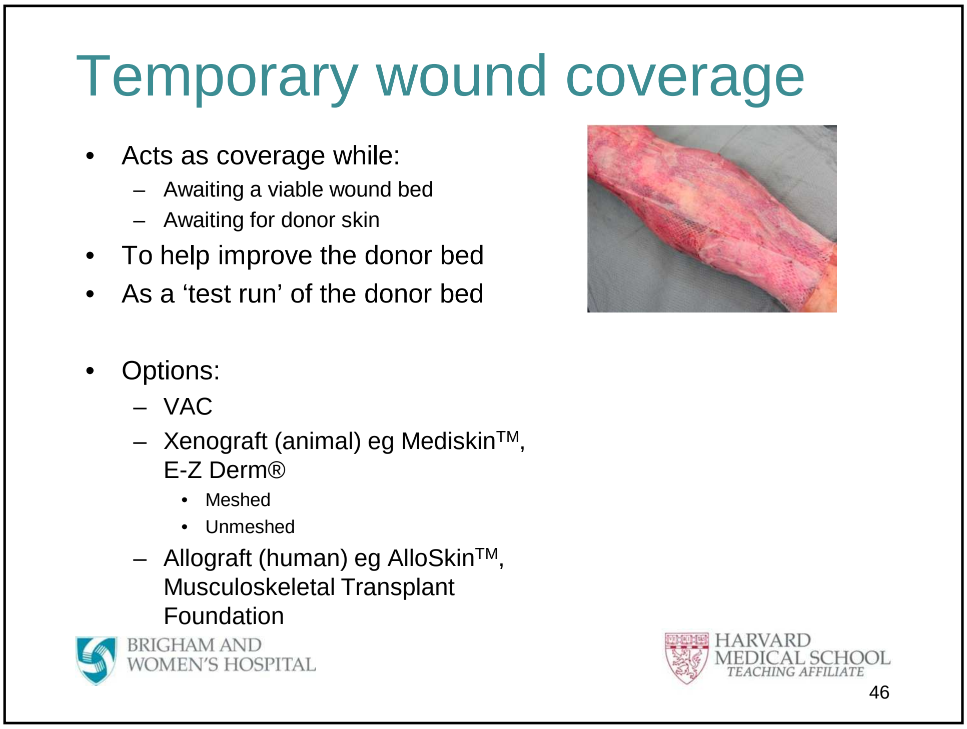


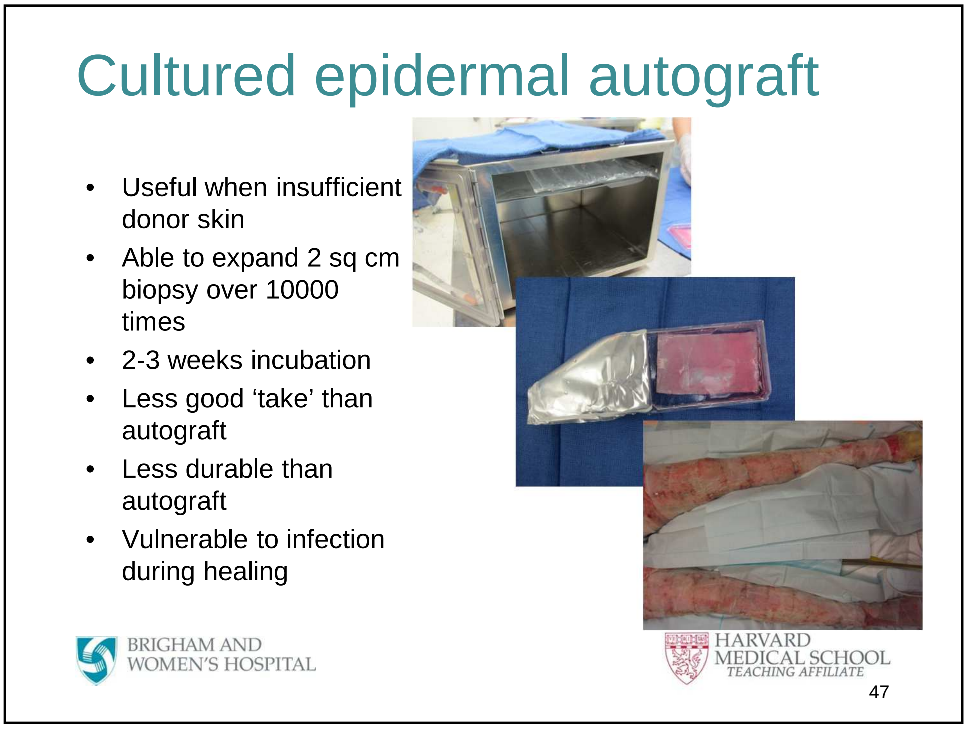
Use of Integra



Temporary wound coverage

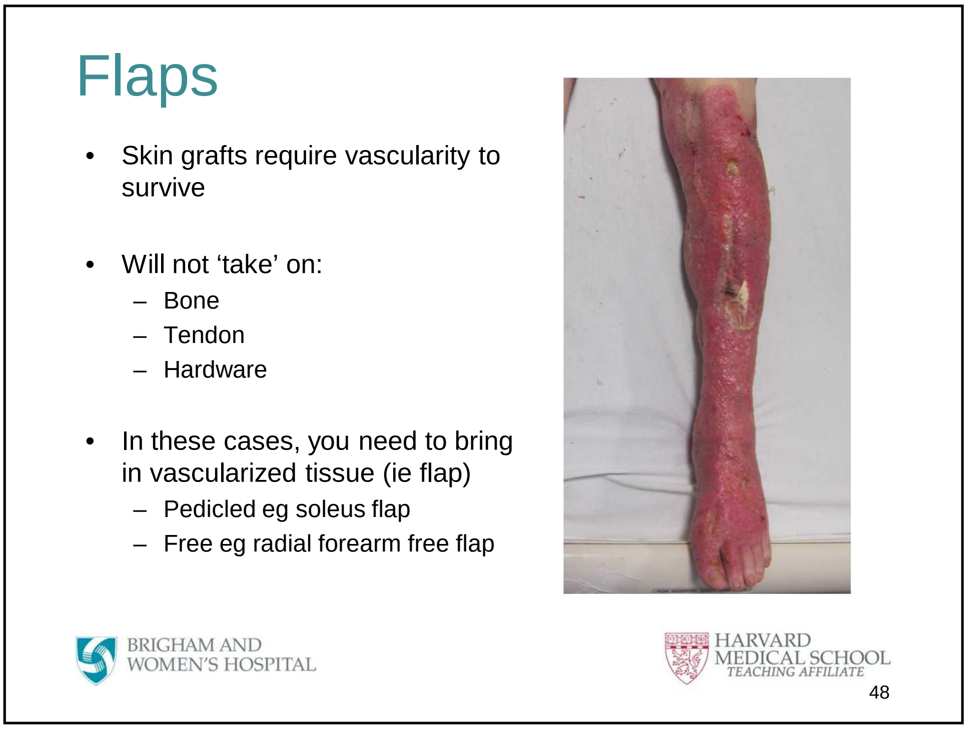
- Acts as coverage while:
  - Awaiting a viable wound bed
  - Awaiting for donor skin
- To help improve the donor bed
- As a 'test run' of the donor bed

- Options:
  - VAC
  - Xenograft (animal) eg Mediskin^{TM}, E-Z Derm®
    - Meshed
    - Unmeshed
  - Allograft (human) eg AlloSkin^{TM}, Musculoskeletal Transplant Foundation



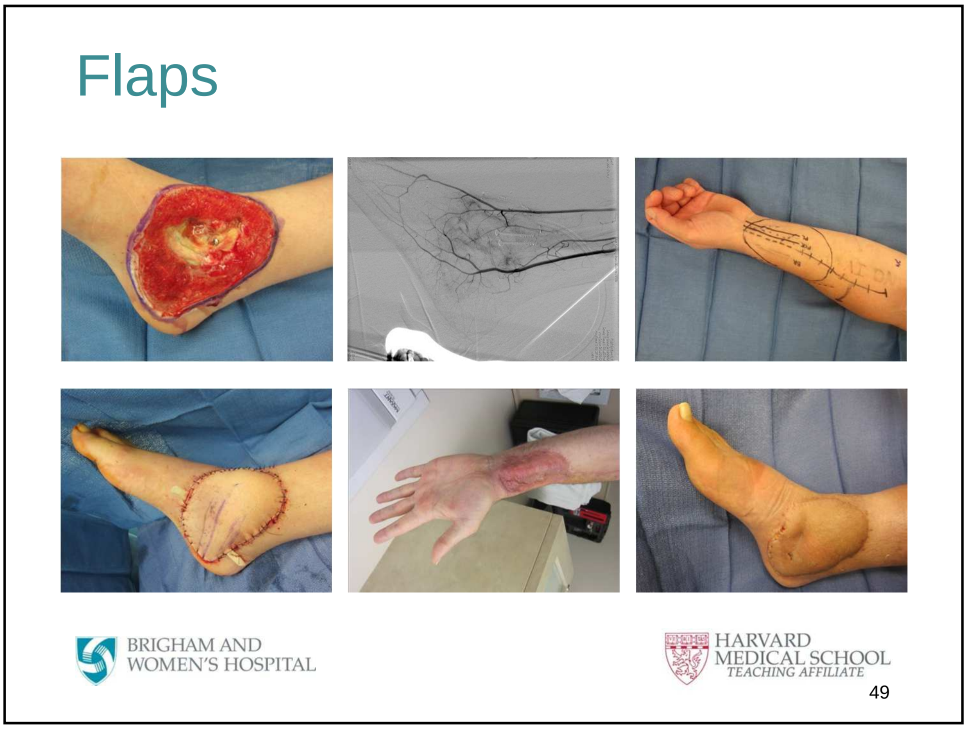
Cultured epidermal autograft

- Useful when insufficient donor skin
- Able to expand 2 sq cm biopsy over 10000 times
- 2-3 weeks incubation
- Less good 'take' than autograft
- Less durable than autograft
- Vulnerable to infection during healing



Flaps

- Skin grafts require vascularity to survive
- Will not 'take' on:
  - Bone
  - Tendon
  - Hardware
- In these cases, you need to bring in vascularized tissue (ie flap)
  - Pedicled eg soleus flap
  - Free eg radial forearm free flap



Flaps

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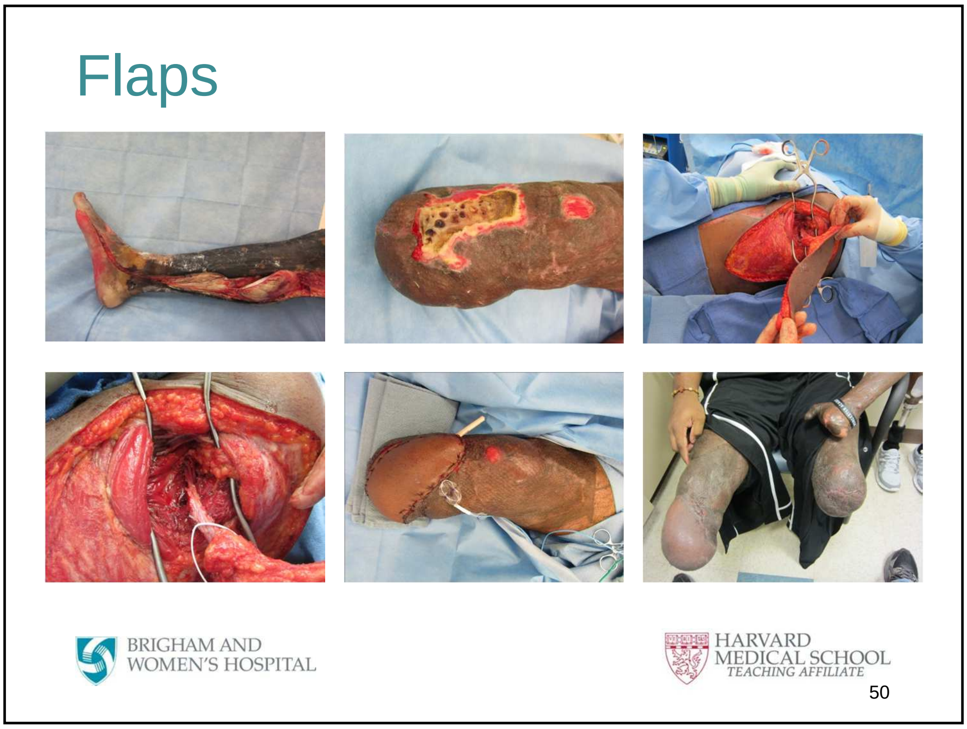
TEACHING AFFILIATE



Flaps

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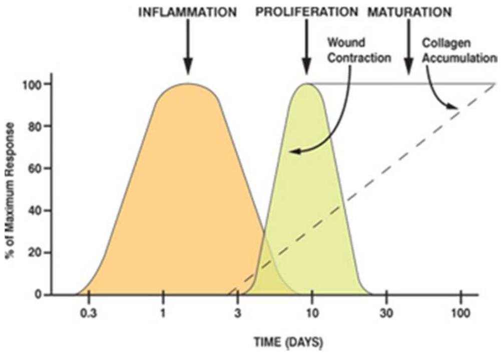
Expected healing

- Depends on:
  - Nutrition
  - Vascularity of wound bed
    - Blood flow
    - Oxygenation
    - Quality of bed
  - Microenvironment
    - Warmth
    - Hydration
  - Distance for diffusion/revascularization
    - Edema
    - Thickness of graft
  - Interface
    - Infection
    - Foreign material
    - Dead tissue
  - Lack of shearing



Source: www.clinimed.co.uk. Hutchinson J (1992). The Wound Programme. Centre for Medical Education: Dundee.

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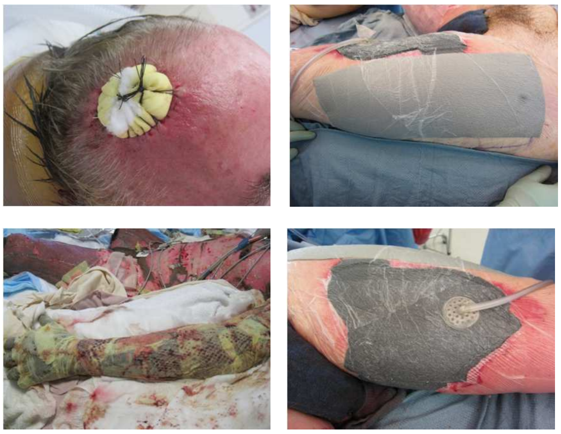
Dressings

- Donor sites
  - Semi-occlusive eg OpSite®, Tegaderm™
  - Antibacterial eg Xeroform
  - Absorbent eg Mepilex®Ag
- Recipient sites
  - NPWT eg Prospera®, VAC®
  - Bolster
  - Xeroform only



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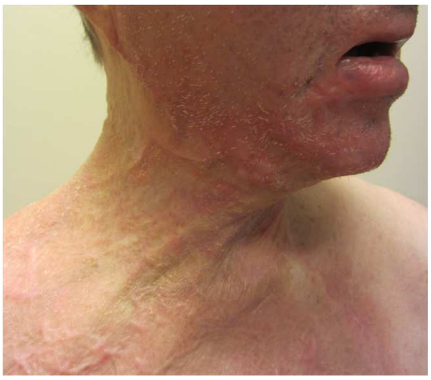
Complications

- Contracture
  - Displacement of tissues eg lip
  - Limited range of joint movement
- Hypertrophic scarring
- Keloid scarring
- Cosmesis

- Prevention is better than cure:
  - Choose the right operation
  - Splint
  - Therapy
  - Compression
  - Silicone
  - Revision surgery (z-plasty, release/graft, flap, laser)



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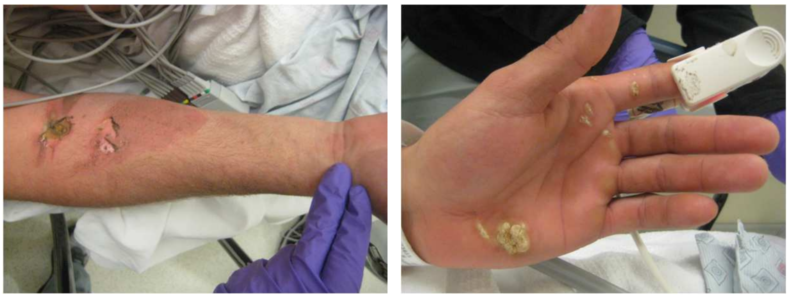
Electrical injuries

- The burn is significantly larger than the skin manifestations
- Risk of compartment syndrome
- May require cardiac monitoring



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ICU management

- Ventilator
  - High risk of VAP
  - Minimization strategies
    - Gastric pH 3.5, semi-recumbent, feeding, chlorhexidine mouth rinse
- Tracheostomy
  - Frequently required due to prolonged ventilation and painful dressings
- Transfusions
  - Transfusions have been shown to increase infection risk
  - No survival correlation for transfusions in the OR
- Infection
  - May be difficult to diagnose – use multiple criteria
- Renal failure
  - Common and associated with high mortality

Nutrition

- Critically important for healing
- Start enteral as soon as practical
  - <24hrs associated with improved outcomes
- Post-pyloric feeding may allow ongoing feeding without need for NPO status with repeated OR trips
- May benefit from oxandrolone

Question 1

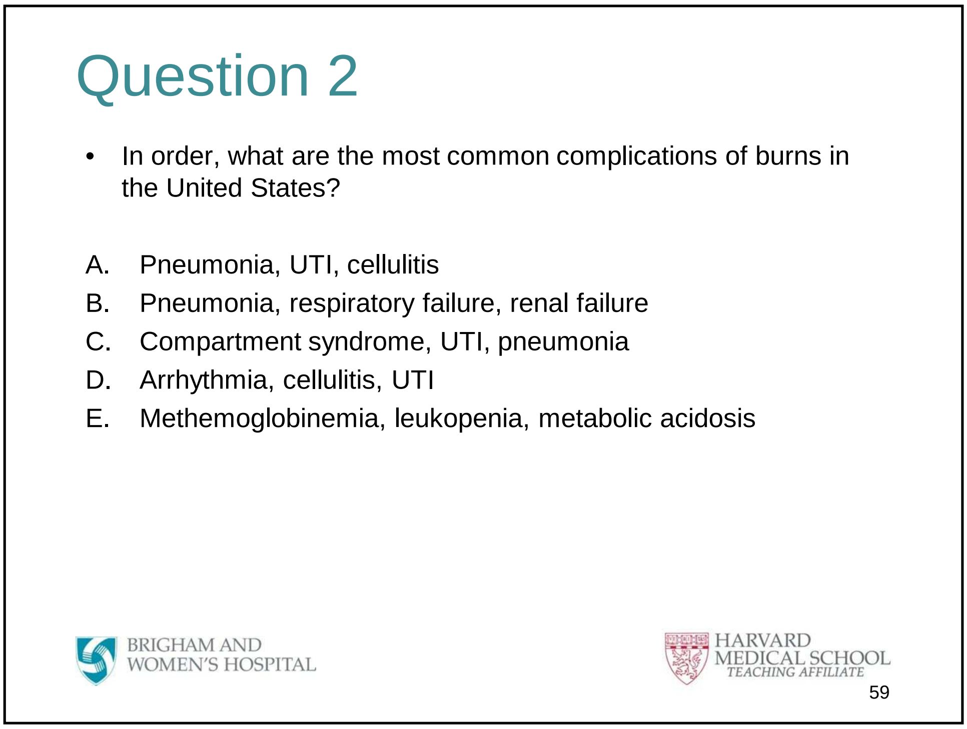
- An 80kg male patient is admitted after a house fire with third degree burns to both legs and one arm and first degree burns to the entire torso. It has taken 4 hours to arrive at the hospital and he has received no fluid. What should his initial fluid rate be?

A. 450
B. 600
C. 1200
D. 1800
E. 14400

Answer 1

- Answer D

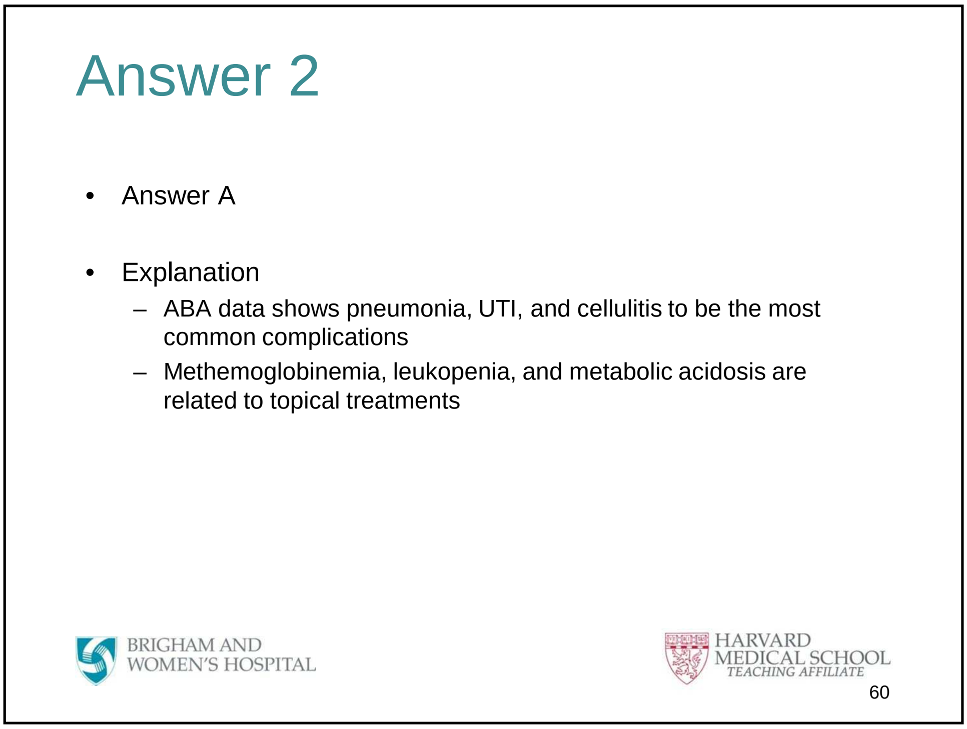
- Explanation
  - Area of burn (Rule of 9s)
    - R leg + L leg + Arm (exclude the first degree burns)
    - 18 + 18 + 9
    - 45
  - Parkland formula
    - 4 x 80 x 45
    - 14400
  - Half should be given in first 8 hours
    - ie 7200 in first 8 hours
  - Four hours have elapsed, so this must be given within the remaining 4h
    - ie 1800cc/h is the initial rate
  - After four hours the rate will drop to 450cc/h



Question 2

- In order, what are the most common complications of burns in the United States?

A. Pneumonia, UTI, cellulitis
B. Pneumonia, respiratory failure, renal failure
C. Compartment syndrome, UTI, pneumonia
D. Arrhythmia, cellulitis, UTI
E. Methemoglobinemia, leukopenia, metabolic acidosis



Answer 2

- Answer A

- Explanation
  - ABA data shows pneumonia, UTI, and cellulitis to be the most common complications
  - Methemoglobinemia, leukopenia, and metabolic acidosis are related to topical treatments

Summary

- Burns are common
- Initial management
  - Start with the ABCs
  - Evaluate for inhalation and CO
  - Resuscitate (Parkland formula)
  - Escharotomies if required
  - Prevent hypothermia
- Diagnosis
  - Area of burn – rule of 9s
  - Depth of burn – pink, red, white
- Treatment
  - Topical antibiotics
  - Early excision and grafting

Useful references

- US Department of Health and Human Services
  - http://chemm.nlm.nih.gov/burns.htm
- American Burn Association
  - http://www.ameriburn.org
- Sood R. Achauer and Sood's Burn Surgery
- Herndon DN. Total Burn Care.
- Rice PL, Orgill DP, Emergency care of moderate and severe thermal burns in adults, UpToDate
  - http://www.uptodate.com

Disclaimer

- I have no proprietary or financial interest in any of the disorders, products, or devices mentioned

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Abdominal Catastrophe and Compartment Syndrome

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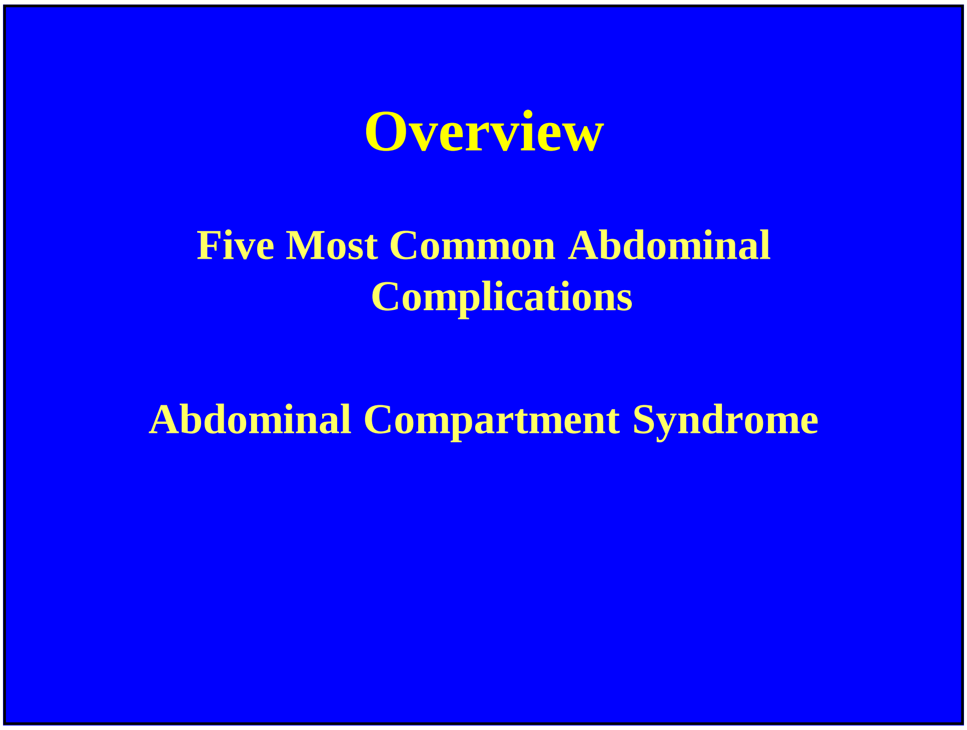
Disclosure

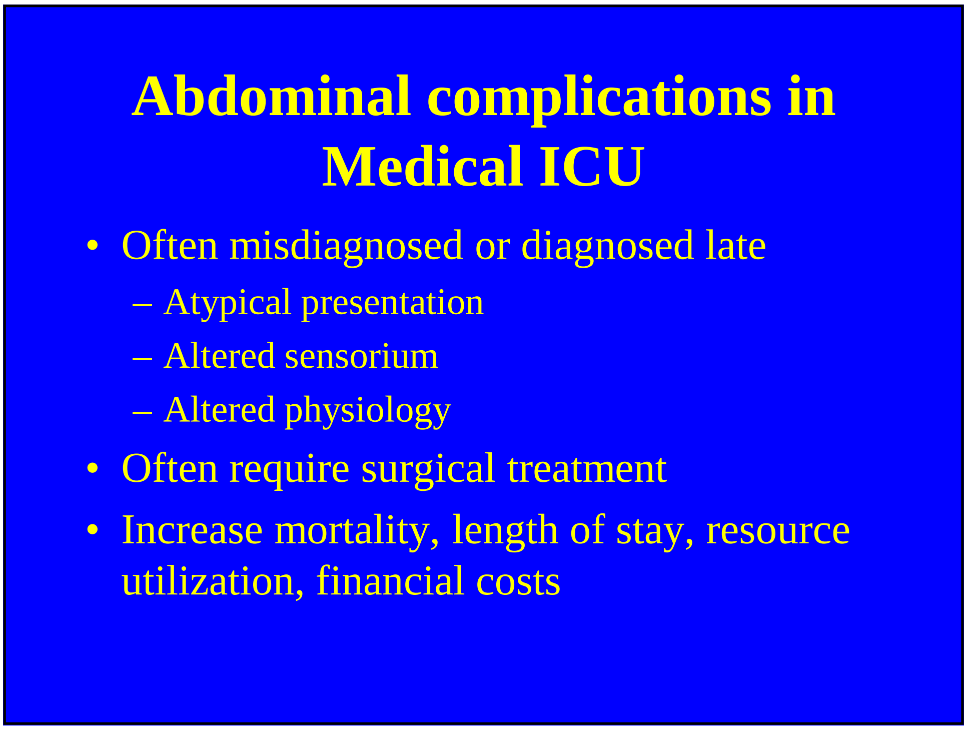
No financial interests in any biomedical or other healthcare-related entities



Overview

Five Most Common Abdominal Complications

Abdominal Compartment Syndrome



Abdominal complications in Medical ICU

- Often misdiagnosed or diagnosed late
  - Atypical presentation
  - Altered sensorium
  - Altered physiology
- Often require surgical treatment
- Increase mortality, length of stay, resource utilization, financial costs

The Fearsome Four

- Mesenteric Ischemia
- Colitis/enteritis
- Cholecystitis
- Perforation

Mesenteric Ischemia

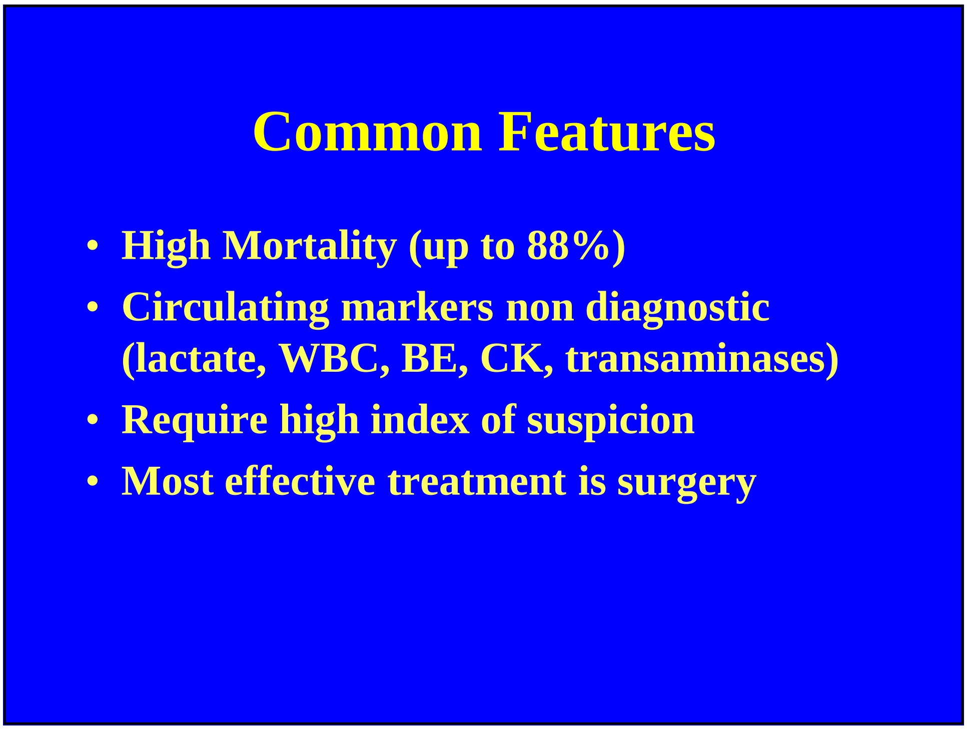
- Most frequently missed diagnosis of the five
- Highest mortality
- Can occur in the absence of arterial occlusive disease (non-occlusive mesenteric ischemia NOMI)

Occlusive Disease

- In the ICU occlusive ischemia and infarction most frequently due to embolism in the setting of atrial fibrillation
- Can be sudden
  - “pain out of proportion”
- Can be insidious
  - Nonspecific abdominal complaints, constipation, melena, , distension, feeding intolerance
- Can progress to fatal sepsis

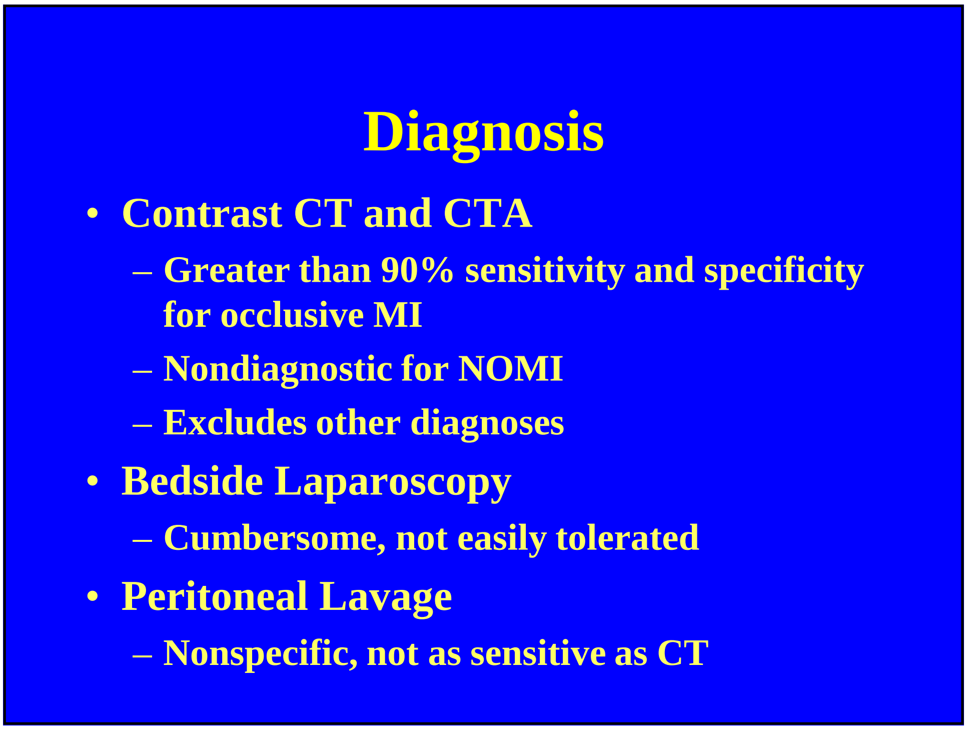
NOMI

- Usually occurs as a consequence of a “low flow state”
  - Heart failure, abdominal compartment syndrome, sepsis of other cause
- Never sudden
- Worsening hypotension, progressive organ failure



Common Features

- High Mortality (up to 88%)
- Circulating markers non diagnostic (lactate, WBC, BE, CK, transaminases)
- Require high index of suspicion
- Most effective treatment is surgery



Diagnosis

- Contrast CT and CTA
  - Greater than 90% sensitivity and specificity for occlusive MI
  - Nondiagnostic for NOMI
  - Excludes other diagnoses
- Bedside Laparoscopy
  - Cumbersome, not easily tolerated
- Peritoneal Lavage
  - Nonspecific, not as sensitive as CT

Treatment

- Occlusive disease almost always requires surgery
- NOMI survival depends on:
  - Correction of underlying illness
  - Resection of necrotic bowel
- To date there is no reliable non invasive test to exclude bowel necrosis

---

Colitis/Enteritis

- C Diff Colitis
  - Exudative inflammatory colitis resulting from Clostridium Difficile
  - Spectrum of presentations
- Fulminant pseudomembranous colitis
  - C difficile colitis with significant systemic toxicity and shock
  - Only 3-5% of all C. diff colitis
  - Mortality >30%

Diagnosis

- Nonspecific abdominal pain and tenderness
- Diarrhea absent in up to 20% of patients
- Leucocytosis
- CT sensitive but not specific
- Stool toxin assay
  - 70% sensitive
- Stool Glutamate dehydrogenase assay (GDH)
  - Sensitive but not specific
- Stool culture
  - Very sensitive, time consuming
- Colonoscopy

Treatment

- Medical therapy for
- nonfulminant Oral vancomycin, oral metronidazole
  - Intravenous metronidazole
  - IVIG- not proven for initial treatment
  - Cholestyramine
- Total abdominal colectomy for fulminant
  - Timing is crucial, mortality increase with delay

Diversion and Lavage

- Small series
- Diagnostic laparoscopy to rule out perforation and construct loop ileostomy
- Lavage colon with PEG
- Vancomycin per stoma, metronidazole iv for 10 days
- 50% survival

Acalculus Cholecystitis

- 1 in 100 patients, depending on ICU population
- Mortality 20-50%
- Results from biliary stasis and chronic distension
  - Sepsis, cardiogenic shock, hemorrhagic shock, fasting
  - Associated with already established organ failure, abdominal hypertension
- Gallbladder wall ischemia
- Necrosis, gangrene present in 44% at diagnosis

Diagnosis

- Few reliable signs or symptoms
  - >90% of patients are already on ventilator
- Fever, leucocytosis, elevation in transaminases not reliable
- Rising bilirubin without ductal dilation in 60% of cases
- Feeding intolerance, worsening organ failure without other cause

Diagnosis

- Ultrasound
  - Gallbladder distension, wall thickening
  - Sludge, rarely calculi
  - Less than 90% sensitivity in most series
- Scintigraphy
  - Often nondiagnostic due to fasting or elevated bilirubin

Diagnosis

- CT with contrast
  - Facilitates diagnosis of infarction and gangrene
  - May reveal or exclude other diagnoses (e.g. mesenteric ischemia)
  - Thickened wall, pericholecystic fluid, sludge, air in gallbladder wall

Treatment

- Cholecystectomy
  - Usually open procedure
  - Higher risk of bleeding and biliary injury
- Percutaneous cholecystostomy
  - Less invasive, less complicated
  - Mortality still high
  - Does not treat gangrene
  - Reasonable option for complicated patients, if detected early

Bowel perforation

- Can occur as a further complication of ischemia, obstruction, or colitis
- Iatrogenic or traumatic
- Does not always cause typical peritonitis, can be insidious
- High mortality
- May present as incidental finding of pneumoperitoneum

Diagnosis

- Diffuse peritonitis (mild or severe)
- New ascites
- Abdominal distension
- Constipation
- Feeding intolerance

Imaging

- Plain radiography is insufficient to exclude perforation
  - Benign pneumoperitioneum
- CT with intravenous contrast
  - High sensitivity
  - Oral contrast not necessary

Treatment

- Almost always surgical
  - Laparotomy, resection, diversion
- Rare cases can be managed without laparotomy
  - Pneumoselective endoscopic perforation
  - Contained perforated diverticulitis
- Delay in surgical treatment increases risk of mortality

Abdominal Compartment Syndrome

- Clinical syndrome the results from elevation in intrabdominal pressure
- Normal IAP is 0-5 mmHg (higher in obesity)
- Can result from acute swelling of the bowel, ascites, hyper-resuscitation, burns, hemoperitoneum etc.
- High mortality (>60%), depending on the cause

Sequelae

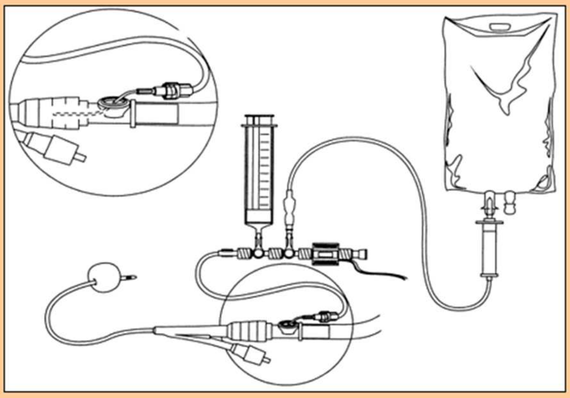
- **High pressure on the abdominal causes higher wall tension, decreased perfusion, and decreased compliance**
  - **Abdominal wall ischemia**
  - **Decreased venous return and impaired cardiac filling (often treated with volume resuscitation)**
  - **Venous engorgement of abdominal viscera, leading to ischemia and bacteremia**
  - **Engorgement of kidneys resulting in AKI**
- **Pressure is exerted on the diaphragm, causing elevated airway pressure, hypoventilation, and respiratory distress**

Diagnosis

- Physical examination
  - Abdominal distension
  - Ascites
  - Respiratory distress, high peak pressure
- Clinical signs of shock and organ failure
- Elevated intrabdominal pressure
- No imaging or other diagnostic testing

Intra abdominal pressure

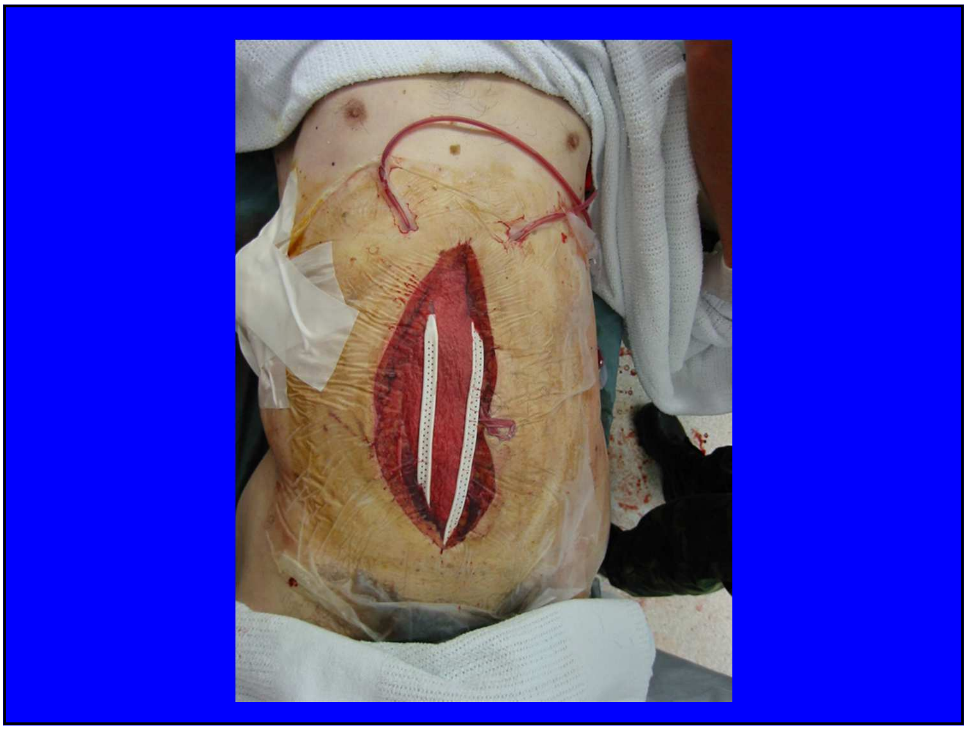
- Most often measured via bladder manometer
  - Can be misleading with pelvic fracture
  - 0-5 mmHg normal
  - >20 mmHg dangerous, may respond to resuscitation temporarily
  - >25 mmHg strongly consider decompression



Bladder pressure transduction system Using a patent Foley catheter with clamped drainage tube, 50 mL sterile water are infused into the bladder via a three-way stopcock system. The badder pressure measured with a transducer correlates well with directly measured intraabdominal pressure.

Decompressive laparotomy

- Long vertical midline laparotomy, temporary abdominal closure
- Immediate effects on ventilatory pressure, venous return and urine output
- Survival depends on underlying cause
  - Established multi-organ failure is unlikely to improve
- Abdominal wall reconstruction can be challenging



Follow up care

- Ongoing pressure monitoring is indicated
- Recurrent compartment syndrome
  - Ongoing swelling or bleeding
  - Incomplete decompression
- Temporary closure may require tightening or loosening

Summary

- Abdominal catastrophes usually appear as complications is already severely ill patients and can herald multiple organ failure
- The most common (ischemia, cholecystitis, colitis, and perforation) carry high mortality and require high clinical suspicion
- CT imaging with intravenous contrast is the most useful diagnostic test
- Surgical treatment where indicated, should be carried out expeditiously, for it to be successful
- High mortality despite advances in management

Review Question 1

What are the most common abdominal complications in critically ill patients?

a) Mesenteric ischemia, colitis, cholecystitis, bowel perforation
b) GI bleeding, intussusception, incarcerated hernia
c) Volvulus, spontaneous bacterial peritonitis, hepatitis
d) Incarcerated hernia, bowel obstruction, appendicitis

Answer Question 1

What are the most common abdominal complications in critically ill patients?

a) Mesenteric ischemia, colitis, cholecystitis, bowel perforation

These complications account for >75% of abdominal complications in ICU patients

Review Question 2

What single imaging modality is most often diagnostic for abdominal catastrophe?

a) Abdominal CT with intravenous contrast
b) Abdominal ultrasound
c) Abdominal MR
d) Endoscopy

Answer Question 2

What single imaging modality is most often diagnostic for abdominal catastrophe?

a) Abdominal CT with intravenous contrast

Intravenous contrast-enhanced CT has the greatest sensitivity for the four common abdominal complications, and can be used to discriminate between them. Oral contrast does not add to the sensitivity or specificity and can be omitted.

Review Question 3

What is a normal intra-abdominal pressure?

a) 0-5 mmHg
b) 5-15 mmHg
c) 15-20 mmHg
d) 20-25 mmHg

Answer Question 3

What is a normal intra-abdominal pressure?

a) 0-5 mmHg

The abdominal pressure is usually low, but may be elevated in obesity or with positive pressure ventilation. Pressures above 20 mmHg are associated with high risk of organ dysfunction.

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Obstetric Critical Care

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HARVARD MEDICAL SCHOOL

- I have no financial relationships to disclose

Objectives

- Understand normal pregnancy physiology and how it may affect management in the ICU setting.
- Review common obstetric scenarios requiring admission to the ICU
  - Hypertensive disease
  - Liver disease
  - Hemorrhage
  - ARDS/ Mechanical ventilation
  - Sepsis
- Special Scenarios
  - ACLS in the pregnant woman
  - Perimortem cesarean delivery

Maternal ICU admissions

- OB patients requiring critical care : 100-900/100,000 [4]
- Risks of ICU admission:
  - Age
  - Race
  - Hospital Acuity
  - Delivery Volume
  - Source of Admission
- Lower mortality rates than the general population [4]
- ~2/3 of deaths occur in women who never reach an ICU [2]

2. Dildy, Gary. Critical Care Obstetrics. 4th ed. Blackwell Science 2004. 4. Soubra, S, Gunupalli, K. Critical illness in pregnancy: an overview. Critical Care Medicine. Volume 33, (10) Supplement. S248-55. October 2005

Maternal ICU Admissions

- Hypertensive diseases: 30.8 % (N=417) of 1354 ICU admits
  - Eclampsia, preeclampsia, HELLP, hypertensive crisis
- Hemorrhage: 20.3% (N=275)
  - Postpartum , abruption, previa
- Pulmonary: 13.0 % (N=176)
  - Pulmonary edema, pneumonia, ARDS, asthma, PE, amniotic fluid embolus

Data summarized from 18 published studies between 1990-2001, Information Modified from Table 1.5 Critical Care Obstetrics, Dildy et al

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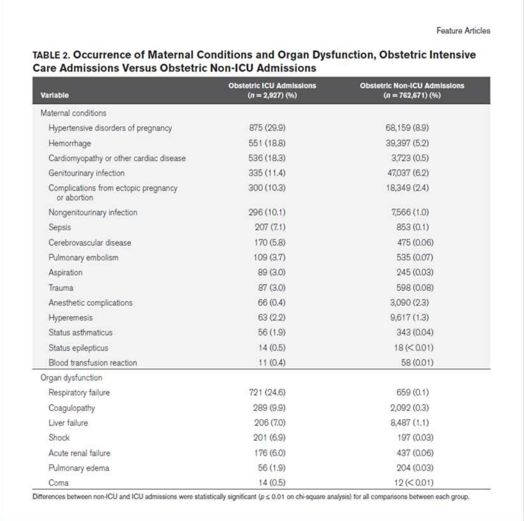
Maternal ICU Admissions

- Need for higher-acuity monitoring
  - More frequent VS assessment
  - Additional monitoring tools
- Need for single-organ support
  - E.g. vasoactive drugs; massive transfusion
  - Alternative: "OB ICU", HDU, ICU
- Need for multi-organ support, mechanical ventilation, or sequelae of resuscitation
  - ICU

Obstetric-Related ICU admissions

- 765K OB admissions
- 698K deliveries
- 2957 admitted to ICU
- Antepartum
  - HTN
  - Trauma
  - Cardiac
- Delivery
  - HTN
  - Hemorrhage
  - Cardiac
- Postpartum
  - Cardiac
  - HTN
  - CVA



Feature Articles

TABLE 2. Occurrence of Maternal Conditions and Organ Dysfunction, Obstetric Intensive Care Admissions Versus Obstetric Non-ICU Admissions

Variable	Obstetric ICU Admissions (n = 2,927) (%)	Obstetric Non-ICU Admissions (n = 762,671) (%)
Maternal conditions		
Hypertensive disorders of pregnancy	875 (29.9)	68,159 (8.9)
Hemorrhage	551 (18.8)	39,397 (5.2)
Cardiomyopathy or other cardiac disease	536 (18.3)	3,723 (0.5)
Genitourinary infection	335 (11.4)	47,037 (6.2)
Complications from ectopic pregnancy or abortion	300 (10.3)	18,349 (2.4)
Nongenitourinary infection	296 (10.1)	7,566 (1.0)
Sepsis	207 (7.1)	853 (0.1)
Cerebrovascular disease	170 (5.8)	475 (0.06)
Pulmonary embolism	109 (3.7)	535 (0.07)
Aspiration	89 (3.0)	245 (0.03)
Trauma	87 (3.0)	598 (0.08)
Anesthetic complications	66 (0.4)	3,090 (2.3)
Hyperemesis	63 (2.2)	9,617 (1.3)
Status asthmaticus	56 (1.9)	343 (0.04)
Status epilepticus	14 (0.5)	18 (< 0.01)
Blood transfusion reaction	11 (0.4)	58 (0.01)
Organ dysfunction		
Respiratory failure	721 (24.6)	659 (0.1)
Coagulopathy	289 (9.9)	2,092 (0.3)
Liver failure	206 (7.0)	8,487 (1.1)
Shock	201 (6.9)	197 (0.03)
Acute renal failure	176 (6.0)	437 (0.06)
Pulmonary edema	56 (1.9)	204 (0.03)
Coma	14 (0.5)	12 (< 0.01)

Differences between non-ICU and ICU admissions were statistically significant ($p \leq 0.01$ on chi-square analysis) for all comparisons between each group.

Wanderer et al, Crit Care Med, 2013

Fetal outcome after maternal admission to ICU

1st trimester
- 65% pregnancy loss,
- spontaneous or induced Ab

2nd trimester
- 43% fetal loss
- 15% adm to NICU

3rd trimester
- 3% fetal loss
- 20% admitted to NICU

- Overall prematurity rate
  - 49%
- Overall fetal death rate
  - 33%

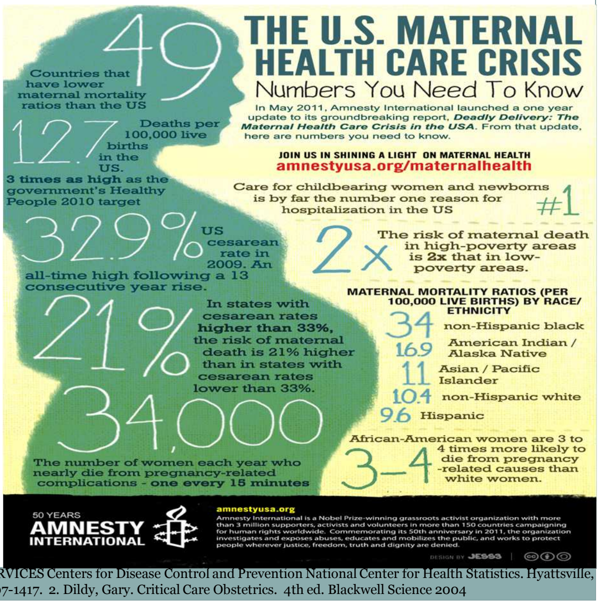
Cartin-Ceba, *CCM* 2008

Maternal Mortality

In 1915, the maternal mortality rate was 607.9 deaths per 100,000 live births [1]

In 2003, the maternal mortality rate was 12.1 deaths per 100,000 live births in the United States [1]

Maternal complications are the fifth leading cause of infant mortality in the U.S. [2]



THE U.S. MATERNAL HEALTH CARE CRISIS

Numbers You Need To Know

In May 2011, Amnesty International launched a one year update to its groundbreaking report, ***Deadly Delivery: The Maternal Health Care Crisis in the USA.*** From that update, here are numbers you need to know.

JOIN US IN SHINING A LIGHT ON MATERNAL HEALTH
amnestyusa.org/maternalhealth

49 Countries that have lower maternal mortality ratios than the US

12.7 Deaths per 100,000 live births in the US. **3 times as high** as the government's Healthy People 2010 target

#1 Care for childbearing women and newborns is by far the number one reason for hospitalization in the US

32.9% US cesarean rate in 2009. An all-time high following a 13 consecutive year rise.

2x The risk of maternal death in high-poverty areas is **2x** that in low-poverty areas.

21% In states with cesarean rates **higher than 33%,** the risk of maternal death is 21% higher than in states with cesarean rates lower than 33%.

MATERNAL MORTALITY RATIOS (PER 100,000 LIVE BIRTHS) BY RACE/ ETHNICITY

34	non-Hispanic black
16.9	American Indian / Alaska Native
11	Asian / Pacific Islander
10.4	non-Hispanic white
9.6	Hispanic

34,000 The number of women each year who nearly die from pregnancy-related complications - **one every 15 minutes**

3–4 African-American women are 3 to 4 times more likely to die from pregnancy-related causes than white women.

50 YEARS AMNESTY INTERNATIONAL

amnestyusa.org
Amnesty International is a Nobel Prize-winning grassroots activist organization with more than 3 million supporters, activists and volunteers in more than 150 countries campaigning for human rights worldwide. Commemorating its 50th anniversary in 2011, the organization investigates and exposes abuses, educates and mobilizes the public, and works to protect people wherever justice, freedom, truth and dignity are denied.

DESIGN BY JESS3

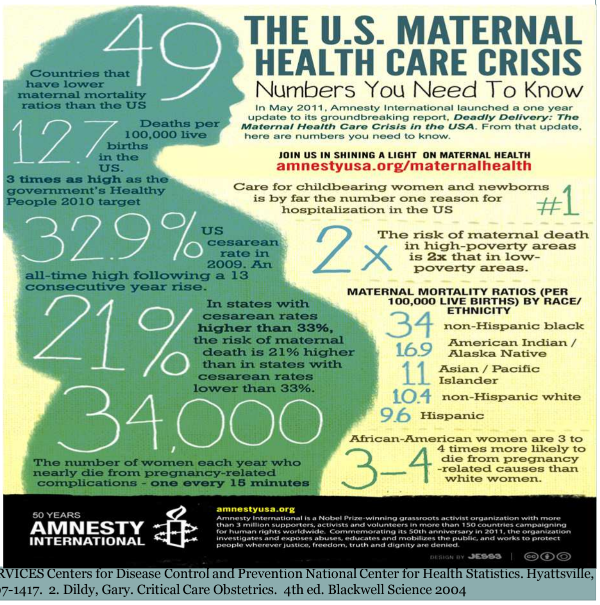
1. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Centers for Disease Control and Prevention National Center for Health Statistics. Hyattsville, MD February 2007 DHHS Publication No. (PHS) 2007-1417. 2. Dildy, Gary. Critical Care Obstetrics. 4th ed. Blackwell Science 2004

Maternal Mortality

Maternal mortality ratios have increased from 6.6 deaths per 100,000 live births in 1987 to 13.3 deaths per 100,000 live births in 2006

The USA spends more than any other country on health care, and more on maternal health than any other type of hospital care

During 2004 and 2005, more than 68,000 women nearly died in childbirth in the USA. Each year, 1.7 million women suffer a complication that has an adverse effect on their health



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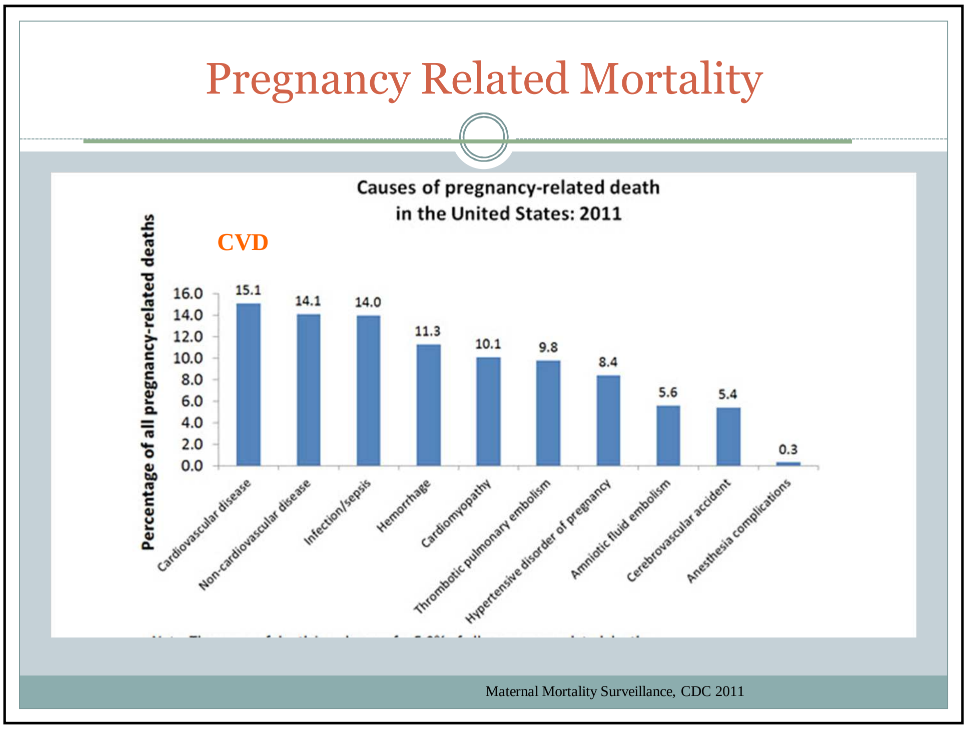
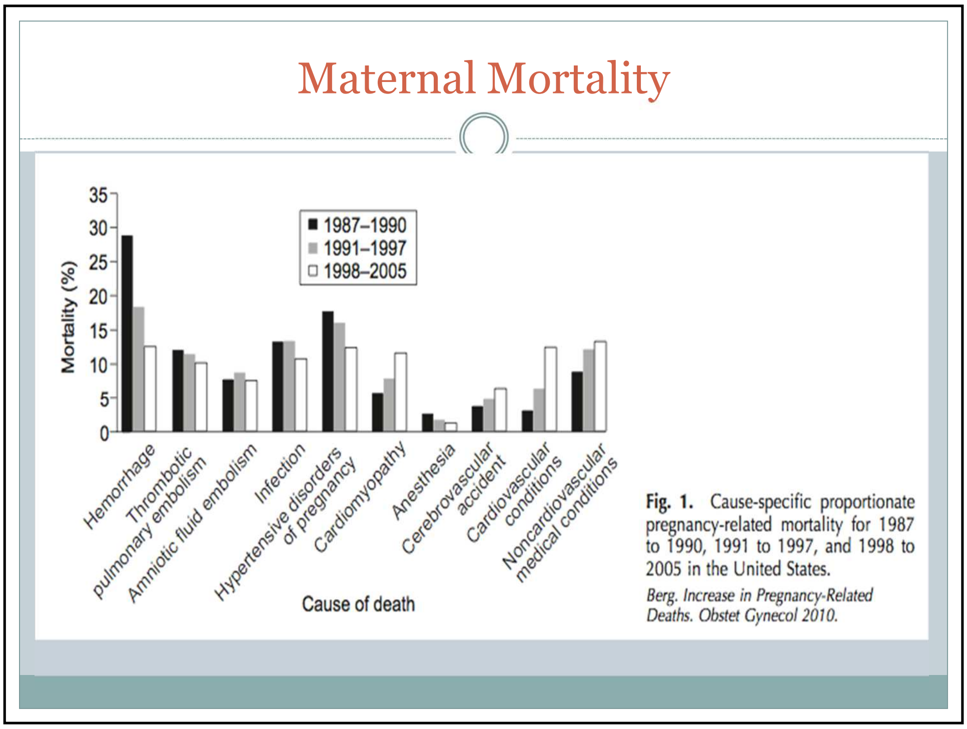


Pregnancy Related Mortality

Maternal Mortality Surveillance, CDC 2011

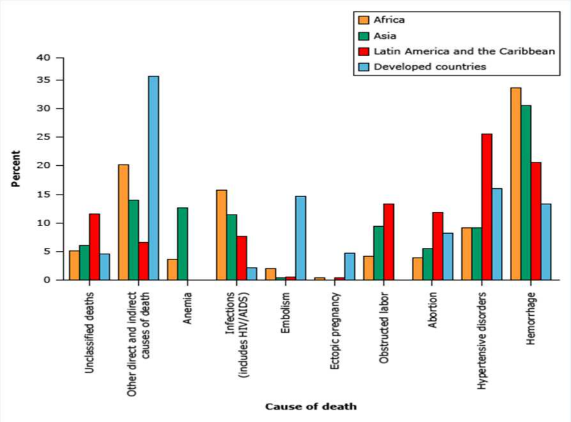


Maternal Mortality

Fig. 1. Cause-specific proportionate pregnancy-related mortality for 1987 to 1990, 1991 to 1997, and 1998 to 2005 in the United States.

Berg. Increase in Pregnancy-Related Deaths. Obstet Gynecol 2010.

Maternal Mortality Worldwide



Prediction of Maternal Mortality

- Several widely used methods:
  - Acute physiologic and chronic health evaluation (APACHE-II, III) scoring system
    - APACHE II most thoroughly studied
  - Simplified acute physiologic score (SAPS)
  - Mortality prediction model (MPM)
  - Sequential Organ Failure Assessment (SOFA)
- None include adjustments for normal obstetric physiology
  - Overestimate mortality risk in the critically ill pregnant woman

Martin, S, Foley, M. Intensive care obstetrics: An evidence-based review. American Journal of Obstetrics & Gynecology.195(3):673-89. September 2006

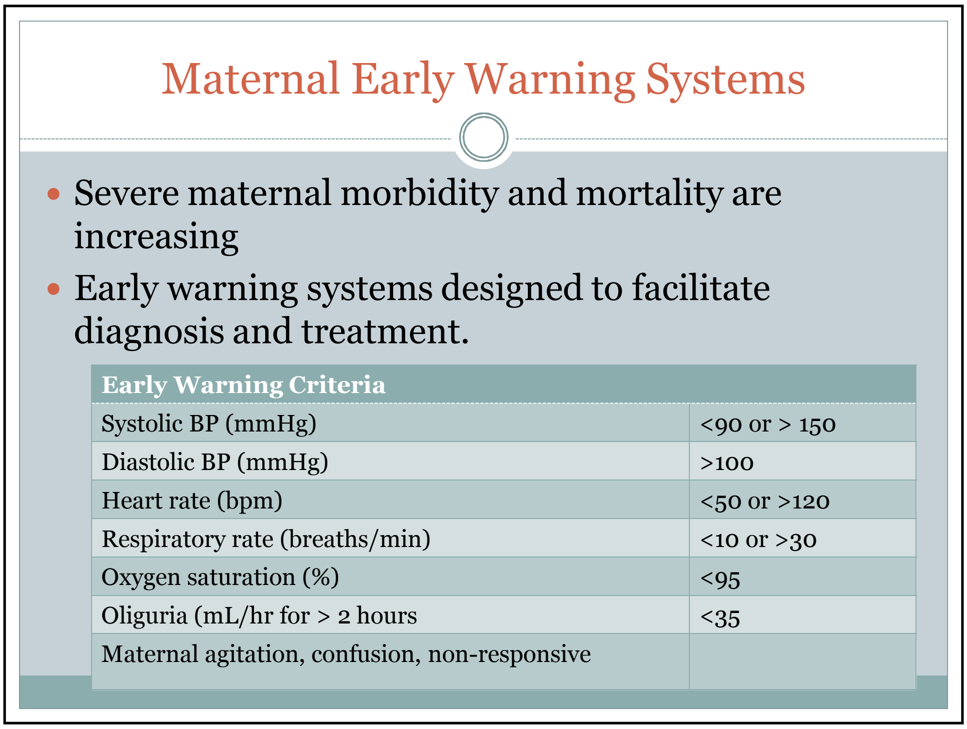
Prediction of Maternal Mortality

- Largest series compared 93 pregnant women with 96 non-pregnant women admitted to the ICU
- Overall mortality rate in the obstetric population was 10.8% and 10.4% in the non-obstetric population
- The APACHE II, SAPS II and MPM II scoring sytems each performed well in the prediction of death (14.7 %, 7.8%, 9.1% respectively
- Each of the 3 scoring tools predicted higher maternal mortality rate for obstetric than non-obstetric patients

Martin, S, Foley, M. Intensive care obstetrics: An evidence-based review. American Journal of Obstetrics & Gynecology.195(3):673-89. September 2006

Prediction of Maternal Morbidity and Mortality

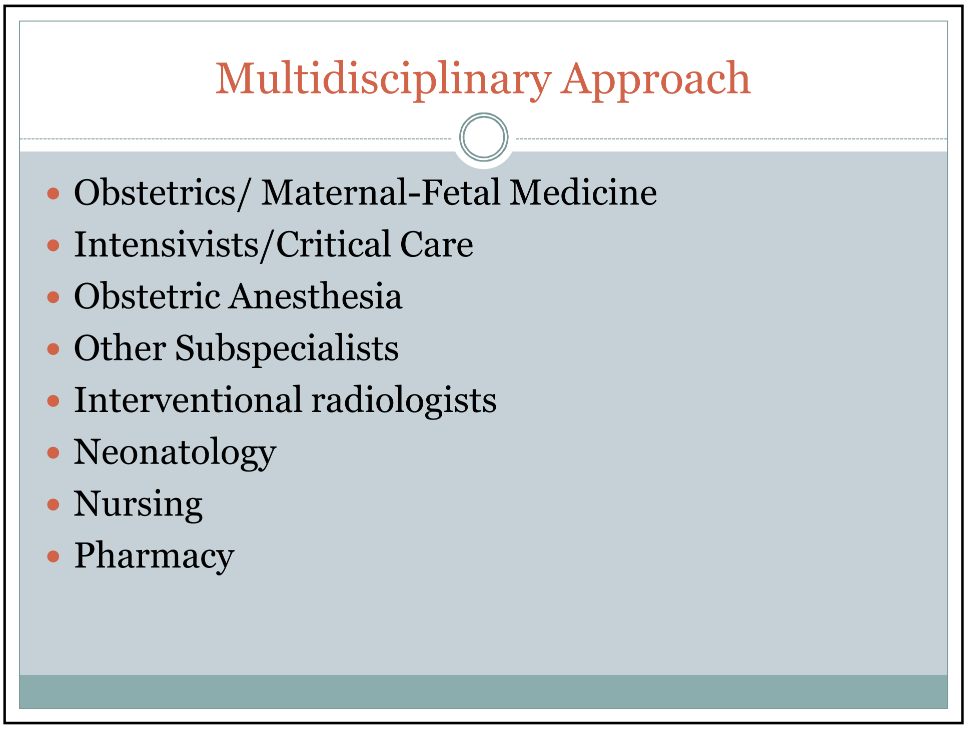
- Use of SOFA and quick SOFA scores in pregnancy have been assessed in multiple small series
- SOFA performs well although sensitivity and specificity varies from study to study
- Some parameters such Pao2/FiO2 may need to have a different cut-off
- No universally accepted obstetric morbidity and mortality score.



Maternal Early Warning Systems

- Severe maternal morbidity and mortality are increasing
- Early warning systems designed to facilitate diagnosis and treatment.

Early Warning Criteria	
Systolic BP (mmHg)	<90 or > 150
Diastolic BP (mmHg)	>100
Heart rate (bpm)	<50 or >120
Respiratory rate (breaths/min)	<10 or >30
Oxygen saturation (%)	<95
Oliguria (mL/hr for > 2 hours	<35
Maternal agitation, confusion, non-responsive	



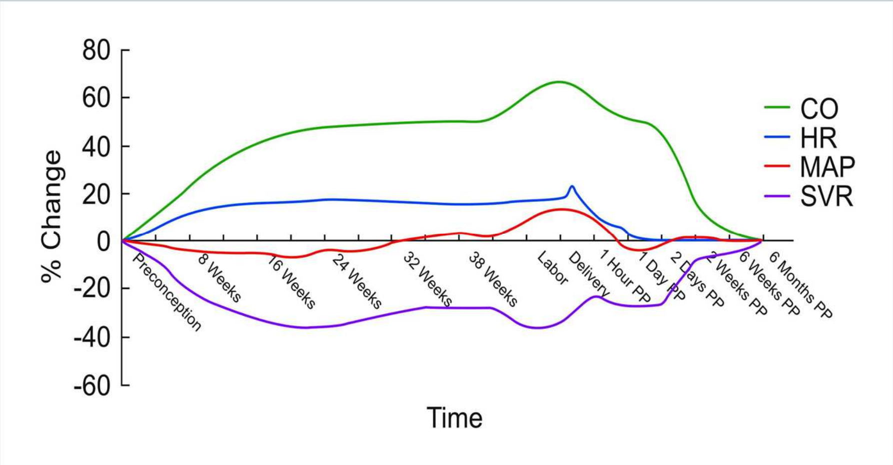
Multidisciplinary Approach

- Obstetrics/ Maternal-Fetal Medicine
- Intensivists/Critical Care
- Obstetric Anesthesia
- Other Subspecialists
- Interventional radiologists
- Neonatology
- Nursing
- Pharmacy

Learning Objectives

- Understand normal pregnancy physiology and how it may affect management in the ICU setting.

Hemodynamic Changes of Pregnancy



Maternal Physiology: Cardiovascular Changes

Measurement	Normal value	Change in pregnancy (%)
Heart rate (beats/min)*	71 ± 10	+10-20
Stroke volume (mL)*	73 ± 9	+30
Cardiac output (L/min)*	4.3 ± 0.9	+30-50 (6 L/min)
Blood volume (L)	5	+20-50
Central venous pressure (mm Hg)*	4 ± 3	Not significant
Pulmonary capillary wedge pressure (mm Hg)*	6 ± 2	Not significant
Systemic vascular resistance (dyne/cm/sec)*	1530 ± 520	−20 (1210 dyne/cm/s)
Pulmonary vascular resistance (mm Hg)*	119 ± 47	−34
Mean arterial pressure (mm Hg)*	86 ± 8	Not significant
Oxygen consumption (mL/min) V02	250	+20-30
COP (mm Hg)*	20.8 ± 1.0	−14
COP - pulmonary capillary wedge pressure gradient (mm Hg)*	14.5 ± 2.5	−28
Left ventricular stroke work index (g/min/m^2)*	41 ± 8	Not significant

Adapted from Clark S, Cotton D, Lee W, Bishop C, Hill T, Southwick J, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161:1439-42; and Elkayam U, Gleicher N. Hemodynamics and cardiac function during normal pregnancy and the puerperium. In: Elkayam U, Gleicher N, editors. Cardiac problems in pregnancy. 3rd ed. New York: Wiley-Liss; 1998. p. 3-19.

Summary of Cardiovascular Changes

- Increased cardiac output (30-50%) and low SVR leads to fall in blood pressure early in the second trimester

- Modest 10-15 bpm increase in heart rate
- Increase effective circulating blood volume 40-50% with corresponding “physiologic” anemia.

Summary of Cardiovascular Changes

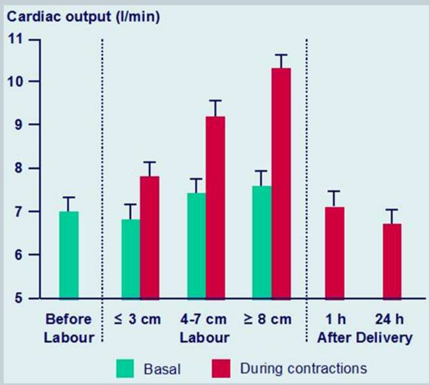
- HR and SV increases in the left lateral recumbent position (increased C.O.)
- Reduced venous return in the supine position can result in the supine hypotensive syndrome
  - Occurs as early as 20 weeks

5. Yeomans, E, Gilstrap, L. Physiologic changes in pregnancy and their impact on critical care. Critical Care Medicine. Volume 33(10) Supplement. pp S256-S258. October 2005

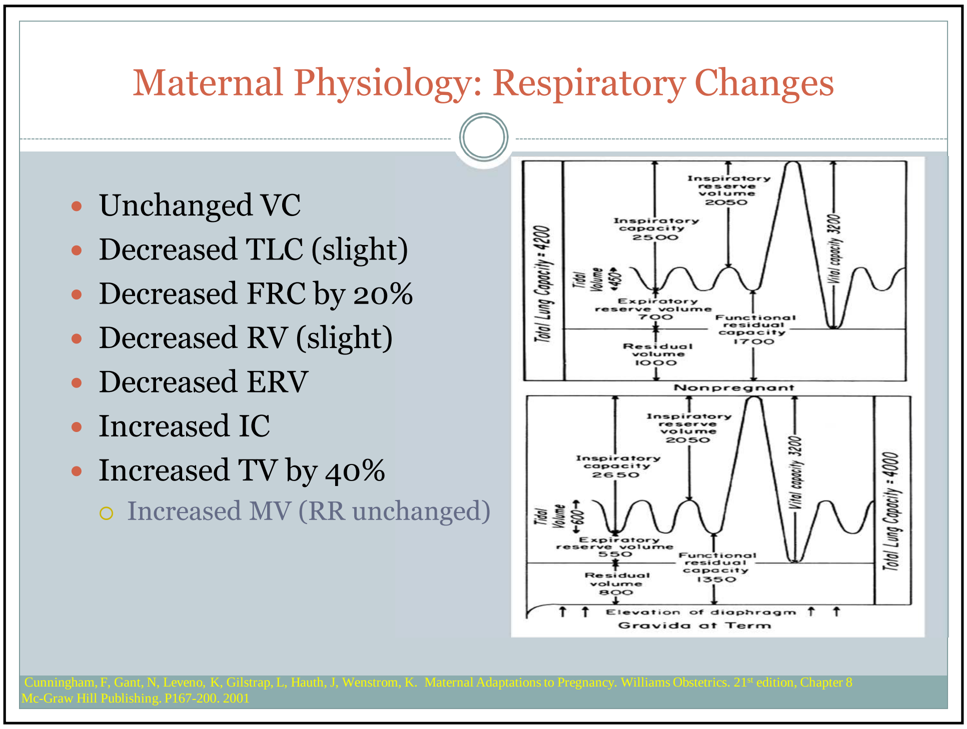
Hemodynamic Changes in Delivery

- Labor:
- ↑ Cardiac output
- ↑ Heart rate
- ↑ Blood pressure
- ↑ Venous return
- ↑ Circulating blood volume with uterine contraction

- Post-partum:
- Autotransfusion from placenta
- ↑ preload and CO



Hunter *Br Heart Journ* 1992

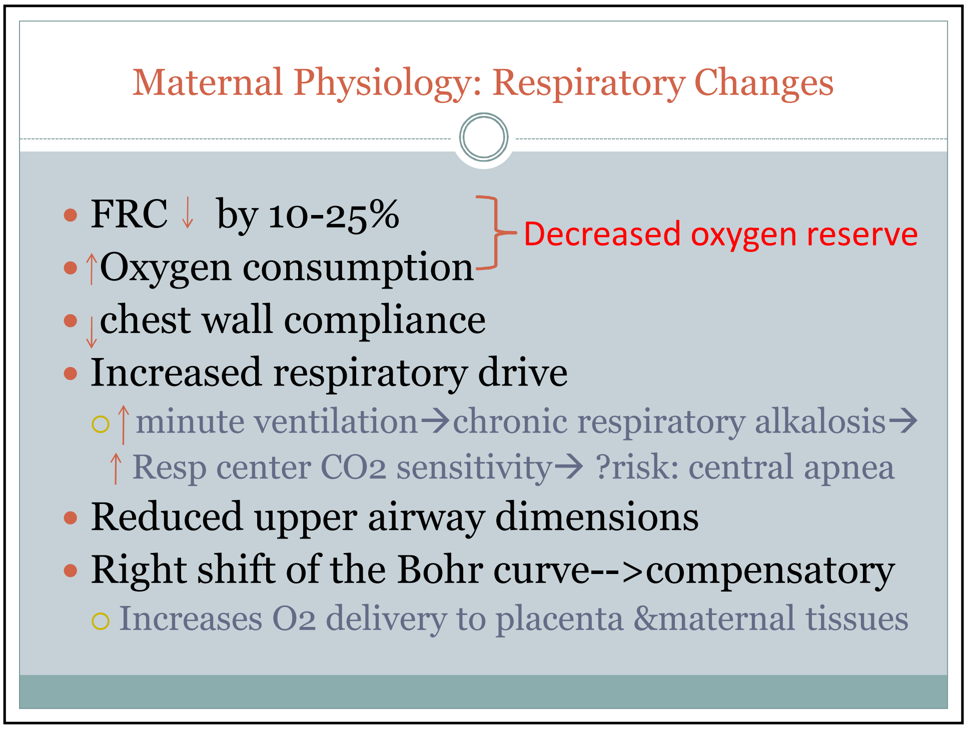


Maternal Physiology: Respiratory Changes

- Unchanged VC
- Decreased TLC (slight)
- Decreased FRC by 20%
- Decreased RV (slight)
- Decreased ERV
- Increased IC
- Increased TV by 40%
    - Increased MV (RR unchanged)

Total Lung Capacity = 4200
Inspiratory reserve volume 2050
Inspiratory capacity 2500
Tidal Volume 450
Vital capacity 3200
Expiratory reserve volume 700
Functional residual capacity 1700
Residual volume 1000
Nonpregnant
Inspiratory reserve volume 2050
Inspiratory capacity 2650
Tidal Volume 600
Vital capacity 3200
Total Lung Capacity = 4000
Expiratory reserve volume 550
Functional residual capacity 1350
Residual volume 800
Elevation of diaphragm
Gravida at Term

Cunningham, F, Gant, N, Leveno, K, Gilstrap, L, Hauth, J, Wenstrom, K. Maternal Adaptations to Pregnancy. Williams Obstetrics. 21st edition, Chapter 8 Mc-Graw Hill Publishing. P167-200. 2001



Maternal Physiology: Respiratory Changes

- FRC ↓ by 10-25%
- ↑Oxygen consumption

Decreased oxygen reserve

- ↓chest wall compliance
- Increased respiratory drive
    - ↑minute ventilation→chronic respiratory alkalosis→ ↑ Resp center CO2 sensitivity→ ?risk: central apnea
- Reduced upper airway dimensions
- Right shift of the Bohr curve-->compensatory
    - Increases O2 delivery to placenta &maternal tissues

Maternal Physiology: ABG Changes

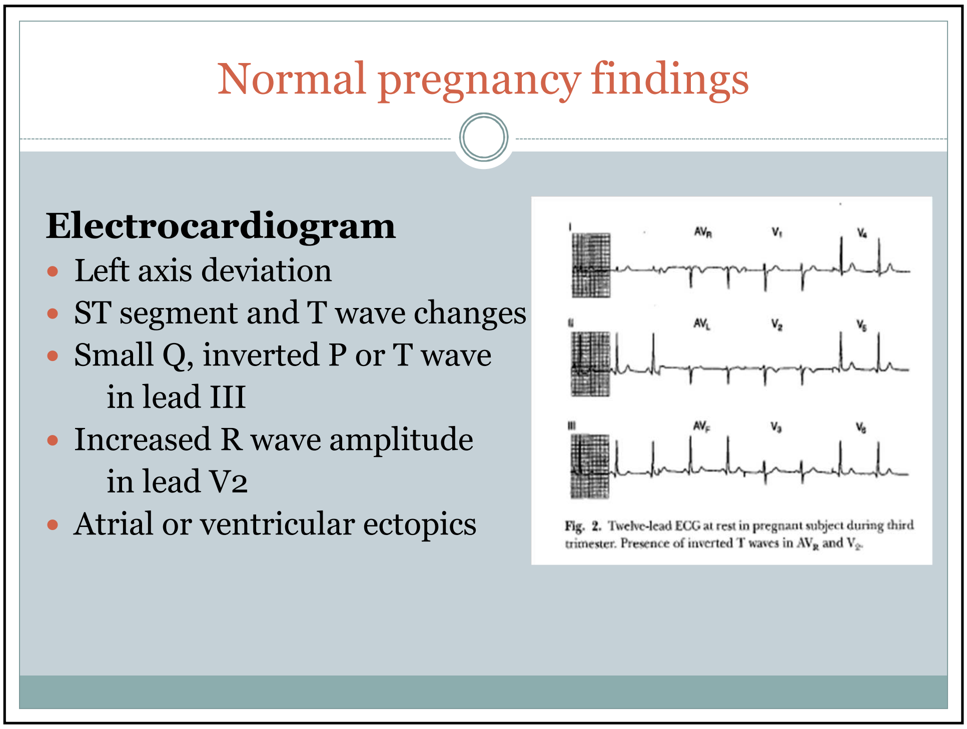
Variable	**Pregnant**	**Nonpregnant**
pH	7.4-7.46	7.38-7.42
Pco_2 (mm Hg)	26-32	38-45
Po_2 (mm Hg)	75-106	70-100
Hco_3^- (mmol/L)	18-21	24-31
Oxygen saturation (%)	95-100	95-100

Respiratory alkalosis with compensatory metabolic acidosis
Is NORMAL in pregnancy

3. Martin, S, Foley, M. Intensive care obstetrics: An evidence-based review. American Journal of Obstetrics & Gynecology.195(3):673-89. September 2006

Maternal Physiology: Respiratory Changes

- 60% of pregnant women experience some sense of shortness of breath which begins as early as the first trimester
- Minute ventilation increases by nearly 50% at term.
- Progesterone-mediated state of chronic hyperventilation and compensated respiratory alkalosis



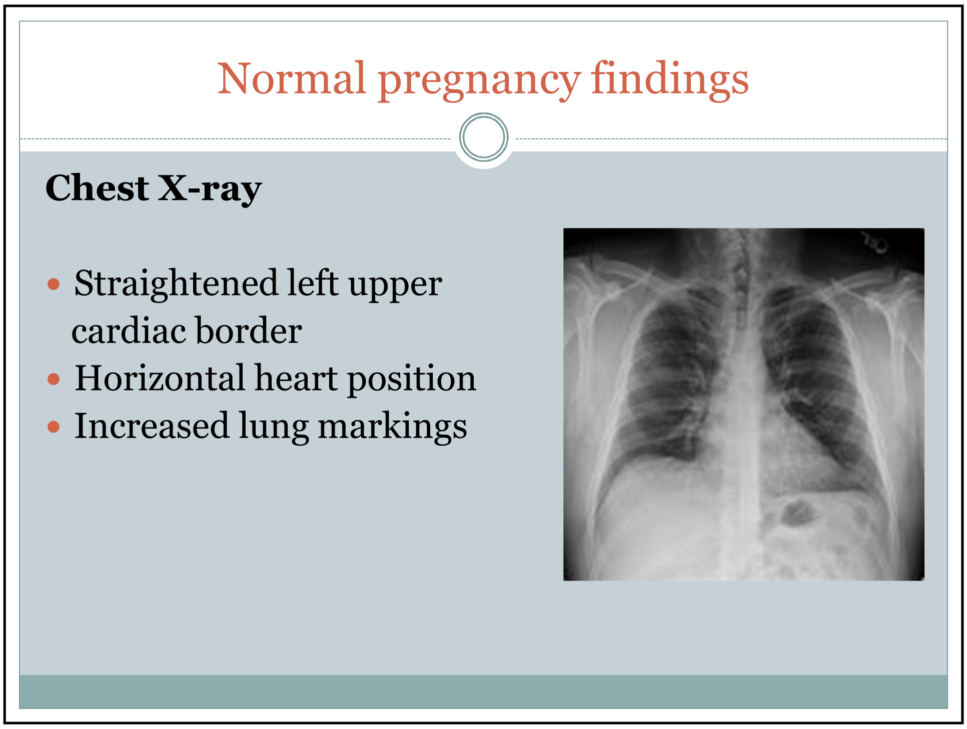
Normal pregnancy findings

Electrocardiogram

- Left axis deviation
- ST segment and T wave changes
- Small Q, inverted P or T wave in lead III
- Increased R wave amplitude in lead V2
- Atrial or ventricular ectopics

I
AVR
V1
V4
II
AVL
V2
V5
III
AVF
V3
V6

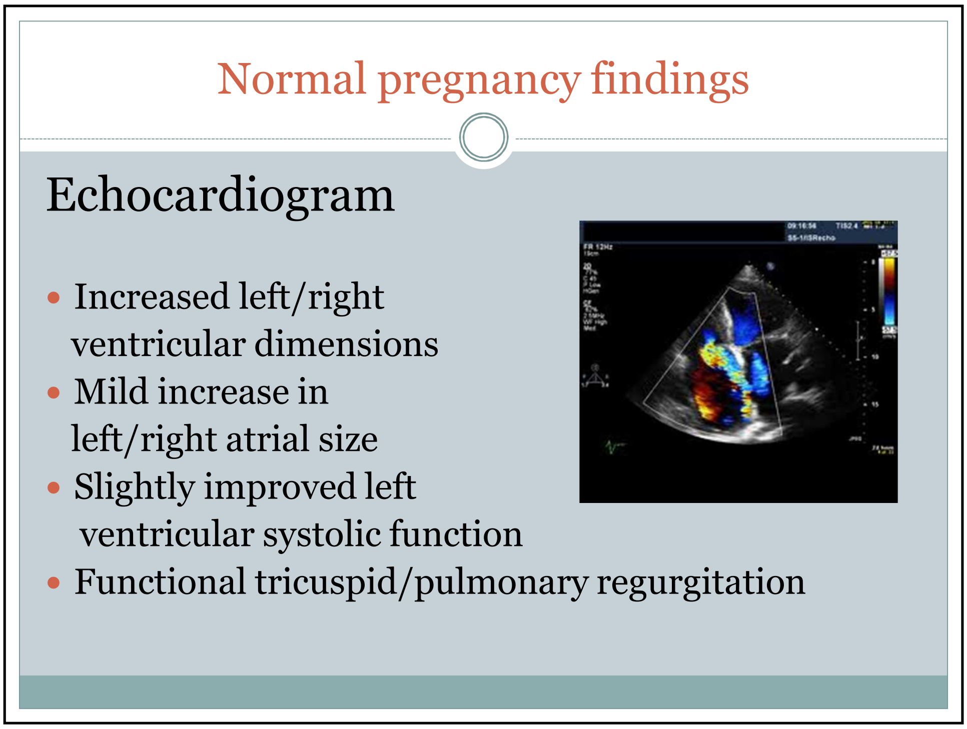
Fig. 2. Twelve-lead ECG at rest in pregnant subject during third trimester. Presence of inverted T waves in AV_R and V_2.



Normal pregnancy findings

Chest X-ray

- Straightened left upper cardiac border
- Horizontal heart position
- Increased lung markings



Normal pregnancy findings

Echocardiogram

- Increased left/right ventricular dimensions
- Mild increase in left/right atrial size
- Slightly improved left ventricular systolic function
- Functional tricuspid/pulmonary regurgitation

Diagnostic Procedures in Pregnancy

- Estimated Fetal Exposure From Some Common Radiologic Procedures
  - Chest X-ray (2 views) 0.02–0.07 mrad
  - Abdominal film (single view) 100 mrad
  - Intravenous pyelography ≥1 rad*
  - Hip film (single view) 200 mrad
  - Mammography 7–20 mrad
  - Barium enema or small bowel series 2–4 rad
  - CT scan of head or chest <1 rad
  - V/Q scan <1 rad
  - CT scan of abdomen and lumbar spine 3.5 rad
  - CT pelvimetry 250 mrad

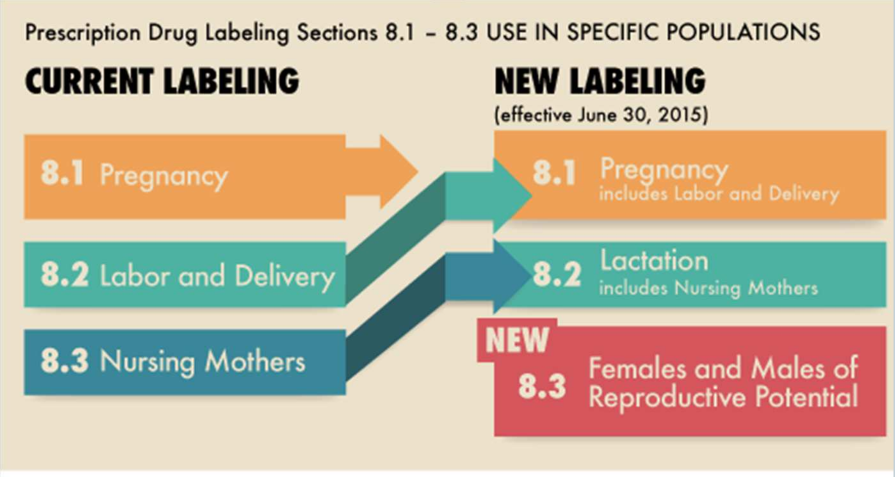
*Exposure depends on the number of films. (>5 rads increases the risk of childhood leukemia) Data from Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC 3rd, Hauth JC, Wenstrom KD. General considerations and maternal evaluation. In: Williams obstetrics. 21st ed. New York (NY): McGraw-Hill; 2001.

Diagnostic Procedures in Pregnancy

- Magnetic resonance imaging safe across all trimesters
  - Recent studies have suggested increase risk of rheumatologic and skin conditions when gadolinium is used in any trimester
  - Small association with stillbirth with use of gadolinium in any trimester

Ray, JAMA 2016 Sep 6;316(9):952-61

Drug Classification in Pregnancy (2015)



Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS

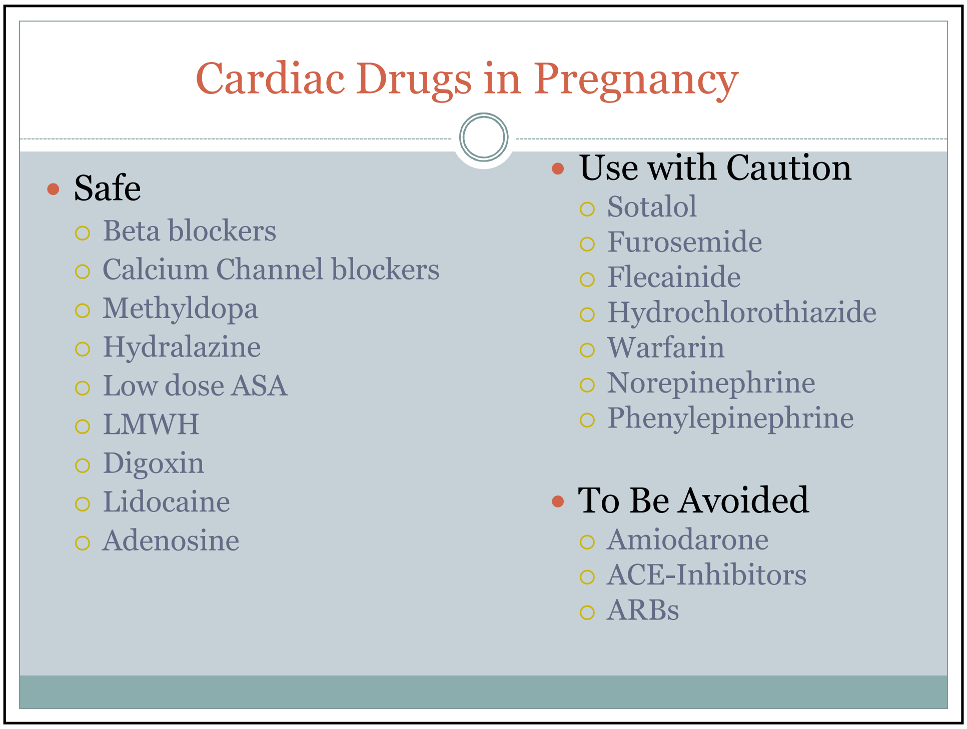
CURRENT LABELING

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers

NEW LABELING

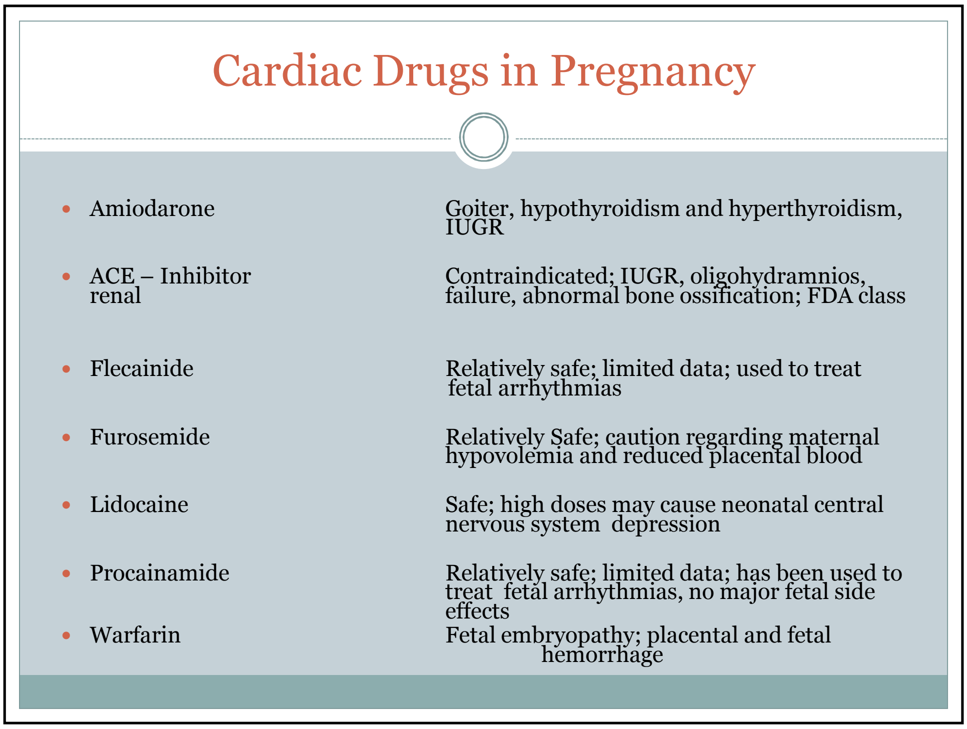
(effective June 30, 2015)

- 8.1 Pregnancy includes Labor and Delivery
- 8.2 Lactation includes Nursing Mothers
- NEW 8.3 Females and Males of Reproductive Potential



Cardiac Drugs in Pregnancy

- Safe
  - Beta blockers
  - Calcium Channel blockers
  - Methyldopa
  - Hydralazine
  - Low dose ASA
  - LMWH
  - Digoxin
  - Lidocaine
  - Adenosine
- Use with Caution
  - Sotalol
  - Furosemide
  - Flecainide
  - Hydrochlorothiazide
  - Warfarin
  - Norepinephrine
  - Phenylepinephrine
- To Be Avoided
  - Amiodarone
  - ACE-Inhibitors
  - ARBs



Cardiac Drugs in Pregnancy

Amiodarone	Goiter, hypothyroidism and hyperthyroidism, IUGR
ACE – Inhibitor renal	Contraindicated; IUGR, oligohydramnios, failure, abnormal bone ossification; FDA class
Flecainide	Relatively safe; limited data; used to treat fetal arrhythmias
Furosemide	Relatively Safe; caution regarding maternal hypovolemia and reduced placental blood
Lidocaine	Safe; high doses may cause neonatal central nervous system depression
Procainamide	Relatively safe; limited data; has been used to treat fetal arrhythmias, no major fetal side effects
Warfarin	Fetal embryopathy; placental and fetal hemorrhage

Learning Objectives

- Understand normal pregnancy physiology and how it may affect management in the ICU setting.
- Review common obstetric scenarios requiring admission to the ICU
  - Hypertensive disease

Hypertension in Pregnancy: Definitions

- Chronic Hypertension
- Gestational Hypertension
- Pre-eclampsia
  - With or without severe features
- Eclampsia
- HELLP
  - Hemolysis, elevated liver enzymes, low platelets

Hypertension in Pregnancy

	Mild HTN	Severe HTN
Preeclampsia	10-25%	50%
Placental abruption	0.5-2%	10%
Fetal growth restriction	12-34 %	30-40%
Preterm birth (<37 weeks)	8-16%	60-70%

Sibai, Obstet and Gynecol 2002; 100:369

Hypertensive disease

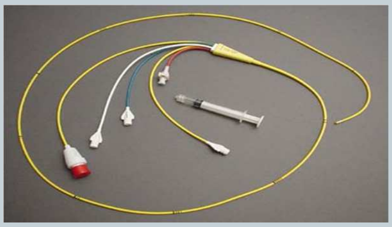
- Limited ability to tolerate hemorrhage
  - Less robust gestational hypervolemia
- Predisposed to pulmonary edema
  - The decrease in COP pressure in pregnancy may be exaggerated in preeclampsia
  - Increased hydrostatic pressure and vascular permeability
- Decrease magnesium infusion rates with impaired renal function
  - Increased GFR→upper limit of serum creatinine of 0.8 mg/dL

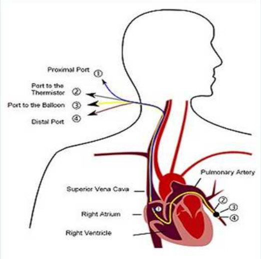
Hypertensive Disease

- “hemoconcentrated state”
  - More susceptible to blood loss at delivery [5]
- Blood volume may expand little, if at all, in severe cases:
  - Study of 44 normal controls vs. 29 eclamptics:
    - Mean BV= 4500 mL controls (+1500 mL nonpregnant)
    - Mean BV= 3200 mL eclamptics (+200 mL nonpregnant) [5]
- Hyper-dynamic cardiac function

5. Yeomans, E, Gilstrap, L. Physiologic changes in pregnancy and their impact on critical care. Critical Care Medicine. Volume 33(10) Supplement. pp S256-S258. October 2005

Hypertensive Disease

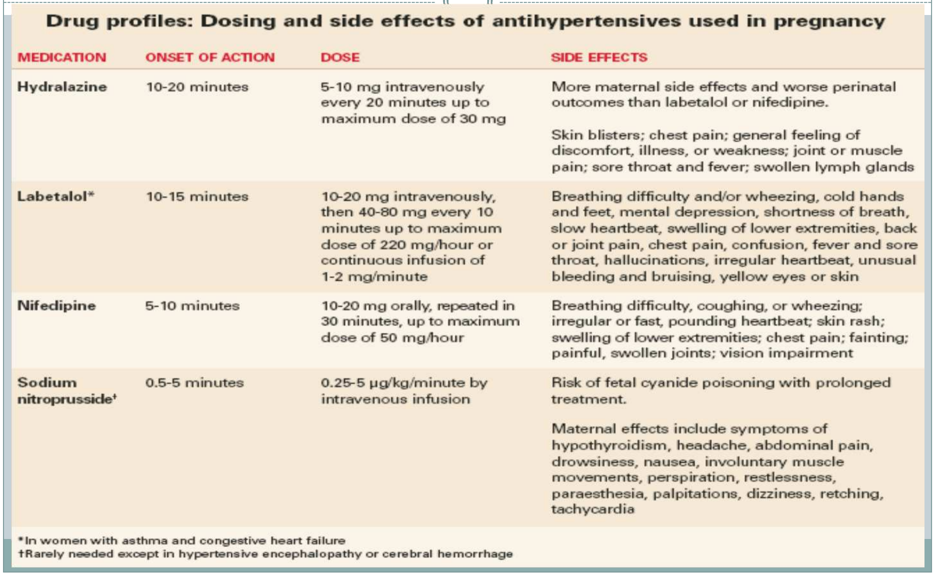



Proximal Port ①
Port to the Thermistor ②
Port to the Balloon ③
Distal Port ④
Pulmonary Artery
Superior Vena Cava
Right Atrium
Right Ventricle
②
③
④

- The PAC-direct monitoring of:
  - CVP (RV preload)
  - PCWP (left ventricular preload)
  - Cardiac output
  - SVR (afterload)
  - PA pressures
  - Mixed venous oxygen saturation
- CVP and PCWP roughly correlate in non-pregnant states, may not be true in pre-eclampsia

Martin, S, Foley, M. Intensive care obstetrics: An evidence-based review. American Journal of Obstetrics & Gynecology.195(3):673-89. September 2006

Medications for the Severely Hypertensive Pregnant Patient



Drug profiles: Dosing and side effects of antihypertensives used in pregnancy

MEDICATION	ONSET OF ACTION	DOSE	SIDE EFFECTS
Hydralazine	10-20 minutes	5-10 mg intravenously every 20 minutes up to maximum dose of 30 mg	More maternal side effects and worse perinatal outcomes than labetalol or nifedipine. Skin blisters; chest pain; general feeling of discomfort, illness, or weakness; joint or muscle pain; sore throat and fever; swollen lymph glands
Labetalol*	10-15 minutes	10-20 mg intravenously, then 40-80 mg every 10 minutes up to maximum dose of 220 mg/hour or continuous infusion of 1-2 mg/minute	Breathing difficulty and/or wheezing, cold hands and feet, mental depression, shortness of breath, slow heartbeat, swelling of lower extremities, back or joint pain, chest pain, confusion, fever and sore throat, hallucinations, irregular heartbeat, unusual bleeding and bruising, yellow eyes or skin
Nifedipine	5-10 minutes	10-20 mg orally, repeated in 30 minutes, up to maximum dose of 50 mg/hour	Breathing difficulty, coughing, or wheezing; irregular or fast, pounding heartbeat; skin rash; swelling of lower extremities; chest pain; fainting; painful, swollen joints; vision impairment
Sodium nitroprusside†	0.5-5 minutes	0.25-5 µg/kg/minute by intravenous infusion	Risk of fetal cyanide poisoning with prolonged treatment. Maternal effects include symptoms of hypothyroidism, headache, abdominal pain, drowsiness, nausea, involuntary muscle movements, perspiration, restlessness, paraesthesia, palpitations, dizziness, retching, tachycardia

*In women with asthma and congestive heart failure
†Rarely needed except in hypertensive encephalopathy or cerebral hemorrhage

Hypertensive Complications

- Severe Pre-eclampsia/ Eclampsia
- Refractory hypertension
- Renal failure
- HELLP/ liver rupture
- Pulmonary edema
- Neurologic sequelae – Seizure, ICH
- Disseminated intravascular coagulation
- Posterior reverse encephalopathy syndrome

Eclampsia

- Airway
- Control convulsions
  - Seizures are self-limited
  - MgSO4 – 2 grams IV bolus to a maximum of 6 grams. Also may be given IM
  - Diazepam 0.1 too.3 mg/kg over 60 seconds. Maximum cumulative dose of 20 mg
- Prevent recurrent seizure with continuous magnesium infusion

HELLP Syndrome

- HELLP occurs in 10-20% of pts w/ preeclampsia
- Diagnosis
  - Microangiopathic hemolytic anemia
  - Platelet count <100,000
  - LDH >600 IU/L, total bili >1.2
  - AST >2x normal
- DIC found in 20% of cases

Differential Dx HELLP

- Thrombotic microangiopathies
    - TTP
    - HUS
- Disseminated intravascular coagulation
- Acute fatty liver of pregnancy
- Malignant hyperthermia
- Systemic lupus erythematosus

TTP-HUS v Preeclampsia

TTP	Preeclampsia
• Significant hemolysis	• Severe HTN
• High LDH	• Liver dysfunction
• Onset prior to 20 weeks gestation	• Increased AST

Management of HELLP

- Stabilize patient, if >34 weeks deliver promptly
- If <34 wks, consider steroids to accelerate FLM then deliver after 48 hours
- $MgSO_4$ for seizure prophylaxis
- Control HTN
- Postpartum: supportive care, correct coagulopathy.
- PRES, hypertensive encephalopathy

HELLP:Antepartum Steroids

- Small observational studies report some prolongation in pregnancy with dexamethasone given antenatally
- No large RCT showing overall improvement in fetal outcome; no maternal benefit
- Experimental; not recommended

HELLP: Postpartum Steroids

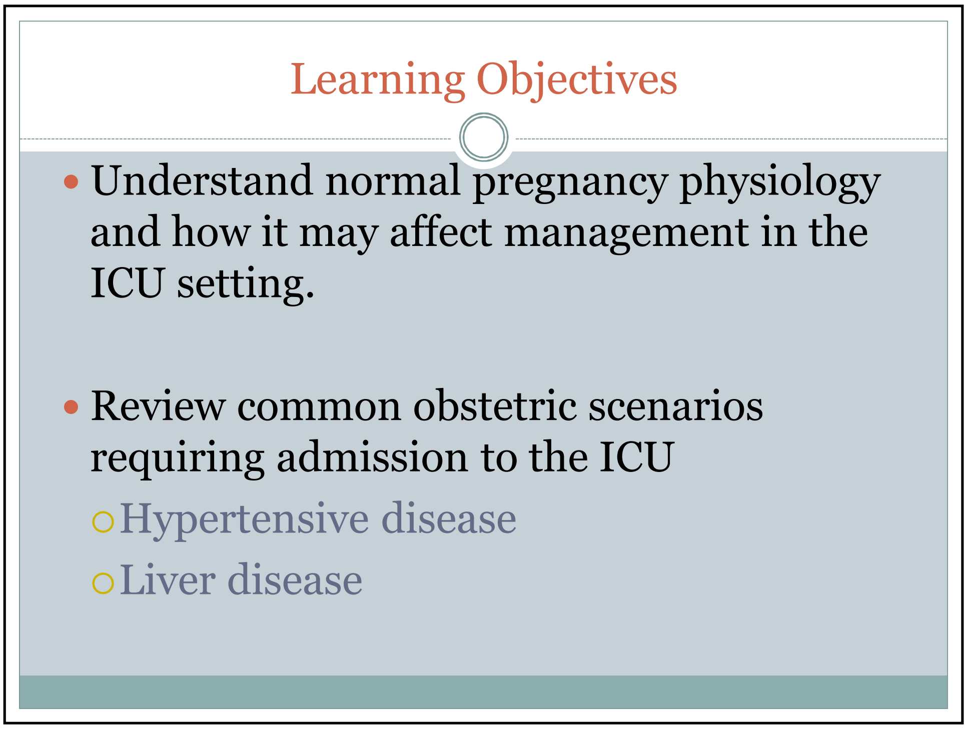
- Small observational studies reported more rapid improvement in labs/clinical parameters
- Fonseca (2005): RCT, 72 pts with HELLP
  - PP Dex did not decrease hosp stay, transfusions, maternal complications, or time to normalization of labs
- Katz (2008): RCT, 114 pts with HELLP
  - PP Dex: no difference in time to resolution of labs, clinical parameters, LOS, maternal complications

HELLP:Maternal-Fetal Outcome

- Maternal Mortality: 1%
- Maternal Morbidity (Sibai 1993)

Abruption	16%
Renal failure	8%
Retinal detachment	1%
Liver hematoma	1%
Liver rupture	rare

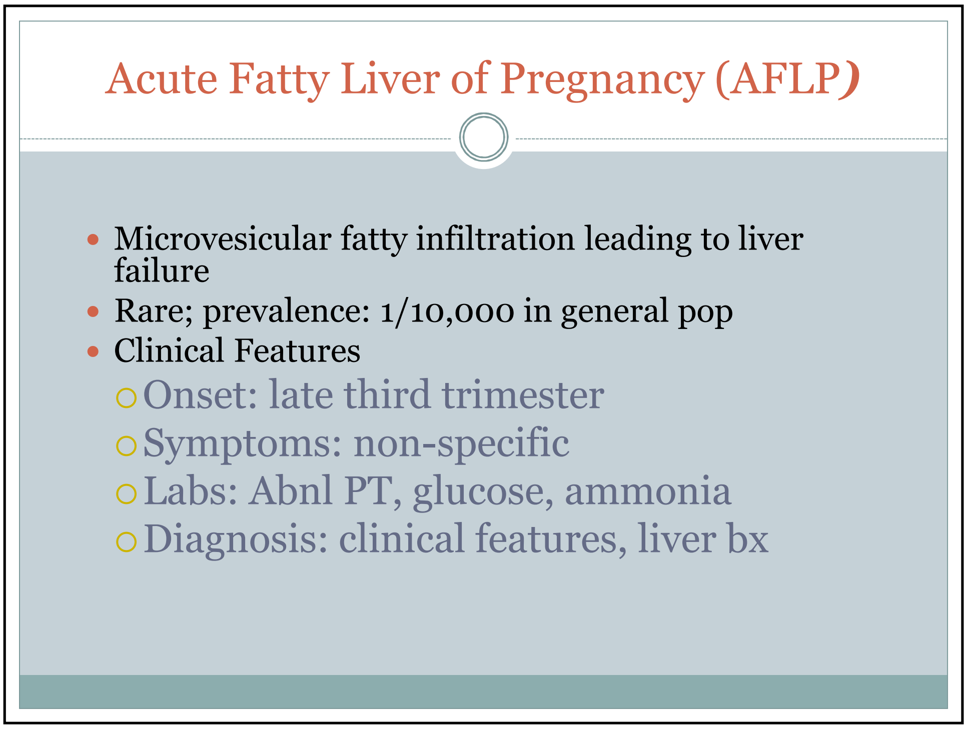
- Perinatal Mortality: 7-20%



Learning Objectives

- Understand normal pregnancy physiology and how it may affect management in the ICU setting.

- Review common obstetric scenarios requiring admission to the ICU
  - Hypertensive disease
  - Liver disease



Acute Fatty Liver of Pregnancy (AFLP)

- Microvesicular fatty infiltration leading to liver failure
- Rare; prevalence: 1/10,000 in general pop
- Clinical Features
  - Onset: late third trimester
  - Symptoms: non-specific
  - Labs: Abnl PT, glucose, ammonia
  - Diagnosis: clinical features, liver bx

AFLP Management

- Establish diagnosis, stabilize patient
- Proceed w/ delivery, C/S for usual OB indication
- Supportive Care
  - Correct hypoglycemia, coagulopathies
  - Renal failure in 60%, dialysis often needed
  - H2 blockers to prevent stress ulcers
  - TPN for tx of pancreatitis
  - Liver transplantation rarely necessary

AFLP Pathogenesis

- Similar to inherited defects in mitochondrial oxidation of fatty acids, esp. long chain defects (LCHAD)
- Treem (1996), Yang (2002), Fearing (2004): Infants homozygous for LCHAD had highest incidence of mothers with AFLP
- Yang (2003): 108 women with AFLP; 19% had identifiable LCHAD mutations

AFLP Outcome

	Maternal Mortality	Fetal Mortality
<1985	72%	63%
>1985	0-5%	10-30%

Davidson, 1995, Sibai, 2005; Knight, 2008

Learning Objectives

- Understand normal pregnancy physiology and how it affects management in the ICU setting.
- Review common obstetric scenarios requiring admission to the ICU
  - Hypertensive disease
  - Liver disease
  - Hemorrhage

Hemorrhage

- SVD: EBL > 500 mL
- C-Section: EBL > 1,000 mL
- Hct drop of 10%
- Delivery EBLs notoriously inaccurate
- Worldwide leading cause of maternal morbidity & mortality

Herbert, W, Zelop, C. Obstetrics and Gynecology. American College of Obstetricians and Gynecologists Practice Bulletin. Postpartum Hemorrhage. Volume 108 (4)Number 76, p1039-1047. October 2006

Post-partum Hemorrhage

Primary/Early	**Secondary/Late**
<24 hours PP	24-12 weeks PP
Uterine atony	Placenta site subinvolution
Retained placenta—especially placenta accreta	Retained products
Defects in coagulation	Infection
Uterine inversion	Inherited coagulation defects

Adapted from Cunningham FG, Leveno KJ, Bloom SL, Hauth JC,Gilstrap L 3rd, Wenstrom KD. Obstetric hemorrhage. In: Williams obstetrics. 22nd ed. New York (NY): McGraw-Hill; 2005. p. 809–54 and Alexander J, Thomas P, Sanghera J. Treatments for secondary postpartum haemorrhage. The Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD002867. DOI: 10.1002/14651858.CD00286

Medical Management

Drug*	Dose/Route	Frequency	Comment
Oxytocin (Pitocin)	IV: 10–40 units in 1 liter Ringer's solution IM: 10 units	Continuous	Avoid undiluted rapid IV infusion, normal saline or lactated which causes hypotension
Methylergonovine (Methergine)	IM: 0.2 mg	Every 2–4 h	Avoid if patient is hypertensive
15-methyl PGF2α (Carboprost) (Hemabate)	IM: 0.25 mg	Every 15–90 min 8 doses maximum	Avoid in asthmatic patients; relative contraindication if hepatic, renal, and cardiac disease. Diarrhea, fever, tachycardia can occur
Misoprostol (Cytotec, PGE1)	800–1,000 mcg rectally	Once	Pyrogenic
Factor VIIa	IV 50-100mcg/kg	Every 2 h until hemostasis	Extremely expensive, No proven benefit in patients without hemophelia
Riastap (Concentrated Human fibrinogen)	IV :calcualte based on fibrinogen level. If unknown 70mg/kg		Stored dehydrated at room temp

Coagulopathic Bleeding

- Lack of functional factors/ platelets
  - Large hemorrhage - dilutional
  - Genetic coagulopathy
  - Blood thinners (lmwh, heparin)
- Disseminated Intravascular Coagulation
  - Abruption
  - Sepsis
  - Amniotic Fluid Embolism

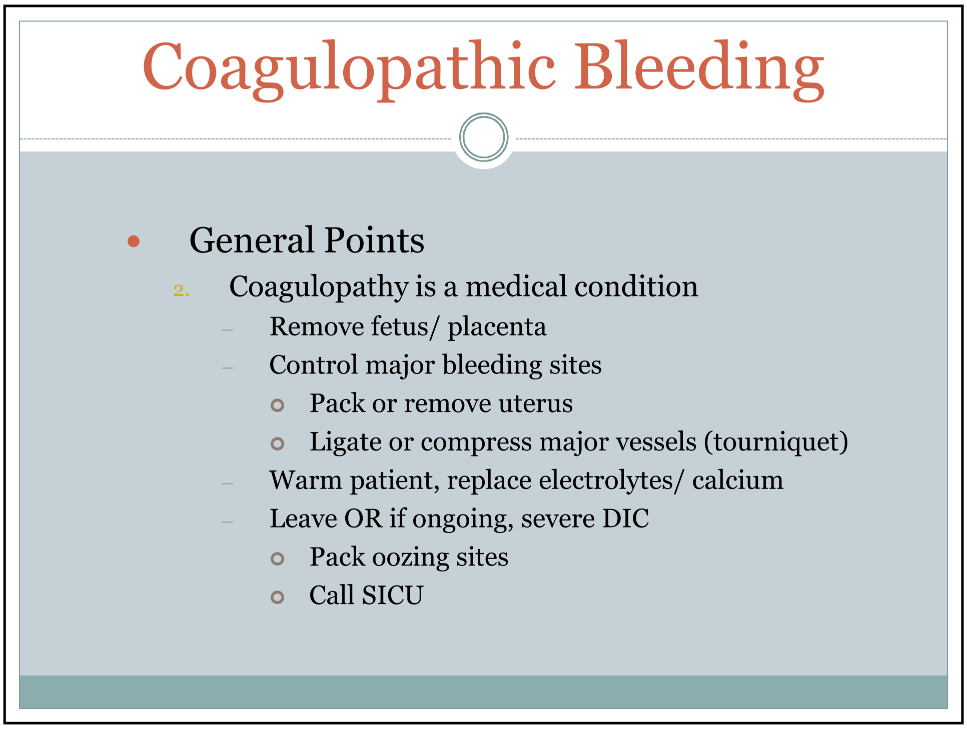
Coagulopathic Bleeding

- Lack of functional factors/ platelets
- Order & replace clotting components
  - FFP, cryoprecipitate, platelets
- Treat underlying condition
- Consult hematology, anesthesiology
- Reverse anticoagulation
  - Protamine, vitamin K

Coagulopathic Bleeding

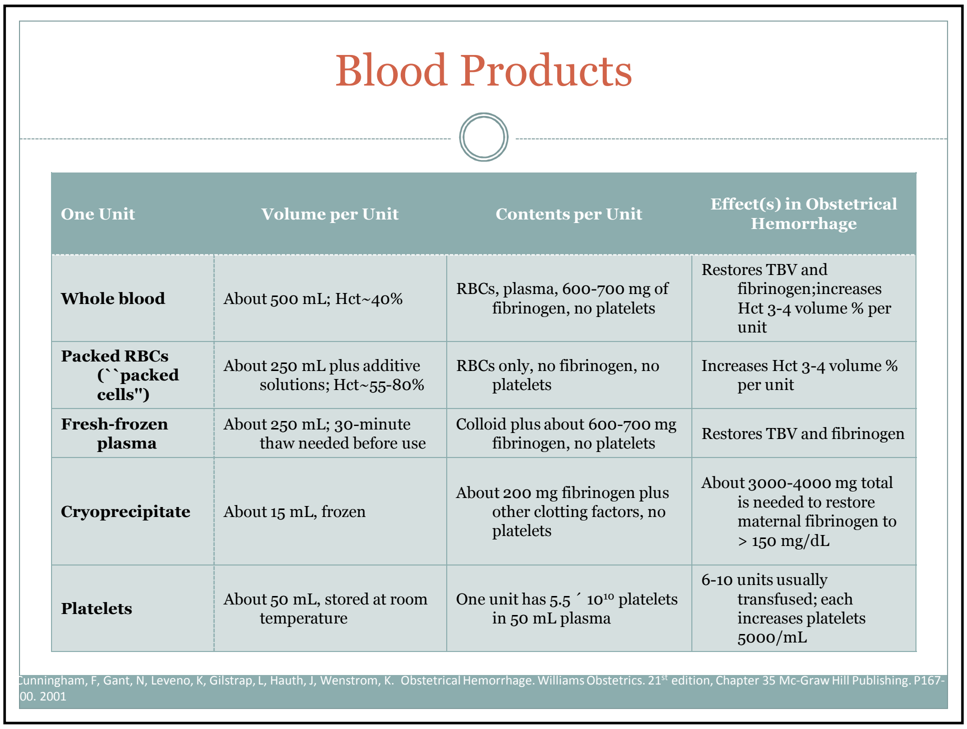
- General Points
  1. Treat based on clinical suspicion
     - Labs take *one hour* to come back
     - Request FFP early
     - Empirically replace plasma, platelets based on degree of hemorrhage & observed bleeding

Fresh Frozen Plasma	Platelets	Cryoprecipitate
•8u blood loss or INR > 1.4 •1u FFP = INR .1	•10u blood loss or count < 40,000 •1u plts = 5-10,000	•Large volume replacements •Does not contain all factors



Coagulopathic Bleeding

- General Points
  2. Coagulopathy is a medical condition
     - Remove fetus/ placenta
     - Control major bleeding sites
       - Pack or remove uterus
       - Ligate or compress major vessels (tourniquet)
     - Warm patient, replace electrolytes/ calcium
     - Leave OR if ongoing, severe DIC
       - Pack oozing sites
       - Call SICU



Blood Products

One Unit	Volume per Unit	Contents per Unit	Effect(s) in Obstetrical Hemorrhage
Whole blood	About 500 mL; Hct~40%	RBCs, plasma, 600-700 mg of fibrinogen, no platelets	Restores TBV and fibrinogen;increases Hct 3-4 volume % per unit
Packed RBCs (``packed cells")	About 250 mL plus additive solutions; Hct~55-80%	RBCs only, no fibrinogen, no platelets	Increases Hct 3-4 volume % per unit
Fresh-frozen plasma	About 250 mL; 30-minute thaw needed before use	Colloid plus about 600-700 mg fibrinogen, no platelets	Restores TBV and fibrinogen
Cryoprecipitate	About 15 mL, frozen	About 200 mg fibrinogen plus other clotting factors, no platelets	About 3000-4000 mg total is needed to restore maternal fibrinogen to > 150 mg/dL
Platelets	About 50 mL, stored at room temperature	One unit has 5.5 ´ 10^{10} platelets in 50 mL plasma	6-10 units usually transfused; each increases platelets 5000/mL

unningham, F, Gant, N, Leveno, K, Gilstrap, L, Hauth, J, Wenstrom, K. Obstetrical Hemorrhage. Williams Obstetrics. 21st edition, Chapter 35 Mc-Graw Hill Publishing. P167-00. 2001

Learning Objectives

- Understand normal pregnancy physiology and how it may affect management in the ICU setting.
- Review common obstetric scenarios requiring admission to the ICU
  - Hypertensive disease
  - Liver disease
  - Hemorrhage
  - Mechanical ventilation

Mechanical Ventilation

- Need for mechanical support in pregnancy is rare
- Retrospective review of 51 patients
  - MV cases: PET (43%) PTL (14%) pneumonia (12%)
  - Maternal mortality rate: 14% (7/51)
  - Perinatal mortality rate: 11% (4/37)
- Limited data on whether or not delivery improves the respiratory status of pregnant patient

Jenkins, T, Troiano, N, Graves, C, Baird, S, Boehm, F. Mechanical ventilation in an obstetric population: Characteristics and delivery rates American Journal of Obstetrics and Gynecology.Volume 188, Issue 2. pp 549-52 February 2003

ARDS

- Supportive Management: [6]
  - Initial stabilization of the patient
  - Confirmation of the diagnosis
  - Assessment of fetal well-being & delivery plan

- Fetal death rate up to 23%, high perinatal asphyxia [6]
  - PaO_2 >70mmHg needed for adequate fetal oxygenation
  - Need PCO_2 gradient of ~10 mmHg to clear fetal CO_2
    - Goal maternal PCO_2 of <45 mmHg, pH >7.30

3. Martin, S, Foley, M. Intensive care obstetrics: An evidence-based review. American Journal of Obstetrics & Gynecology.195(3):673-89. September 2006
6. Cole, D, Taylor, T, McCullough, D, Shoff, C, Derdak, S. Acute respiratory distress syndrome in pregnancy. Critical Care Medicine. Volume 33(10) Supplement. pp S269-78. October 2005

Obstetrical issues in ARDS

- Maternal survival in ARDS is not improved by delivery
- Fetal survival is clearly gestational-age-dependent
- Delivery may, however, simplify management
  - Reasonable option after 32 weeks or any time maternal or fetal condition deteriorating
  - Neonatal outcomes improved with antenatal steroids (48 hour course)

ARDS in Pregnancy

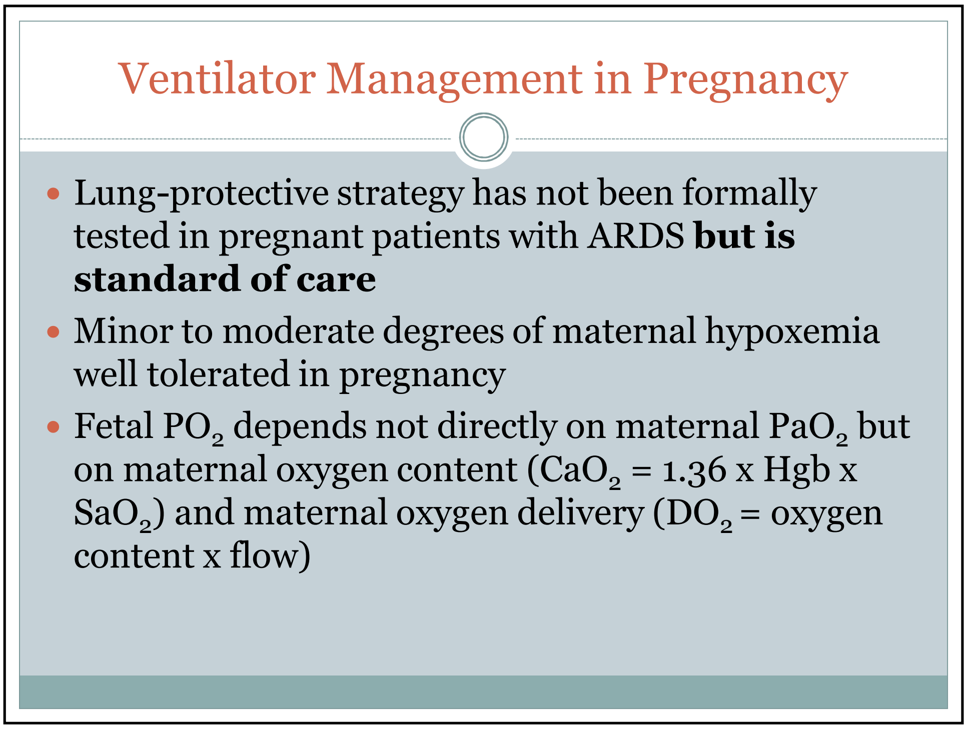
- Increased work of breathing with ARDS shunts blood away from the uterus
- Over-use of PEEP decreases CO by decreasing preload
- Remember, pregnancy norms for ventilation are different:
  - Higher MV
  - Decreased FRC
  - Lower chest wall compliance
  - Compensated respiratory alkalosis

- How well is acidemia tolerated?
- What does the maternal-fetal P_{CO_2} gradient need to be?

Ventilator management in ARDS

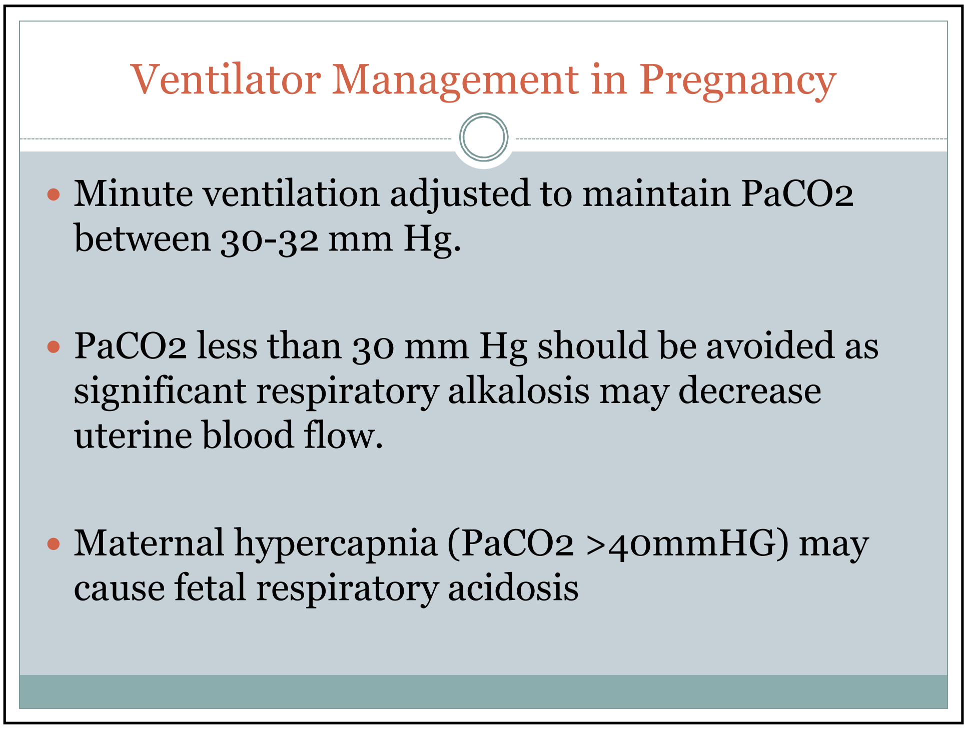
- ~~Classical strategy:~~
  - ~~Normalize PaCo2 & PaO2~~
  - ~~Set tidal volume 10-15 ml/kg~~
  - ~~PEEP as needed (up to 20 cm H2O)~~
  - ~~Barotrauma risk~~
- **Lung-protective:**
  - **Minimize barotrauma**
  - **Set TV 5-8 ml/kg (PBW)**
  - **Longer inspiratory times**
  - **Permissive hypercapnia**
  - **Allow pH to decrease**
  - **Bicarb only if acidosis compromises patient**
  - **PEEP 5-24 cm H_2O, fixed combination w FIO_2**

ARDSNet, *NEJM* 2000



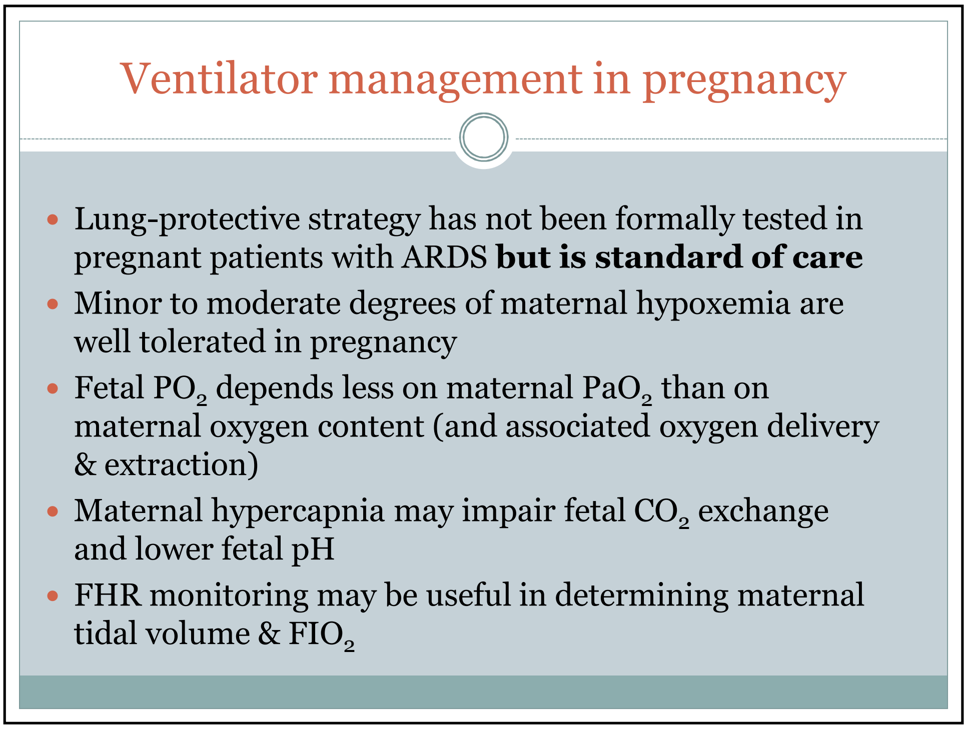
Ventilator Management in Pregnancy

- Lung-protective strategy has not been formally tested in pregnant patients with ARDS **but is standard of care**
- Minor to moderate degrees of maternal hypoxemia well tolerated in pregnancy
- Fetal PO_2 depends not directly on maternal PaO_2 but on maternal oxygen content (CaO_2 = 1.36 x Hgb x SaO_2) and maternal oxygen delivery (DO_2 = oxygen content x flow)



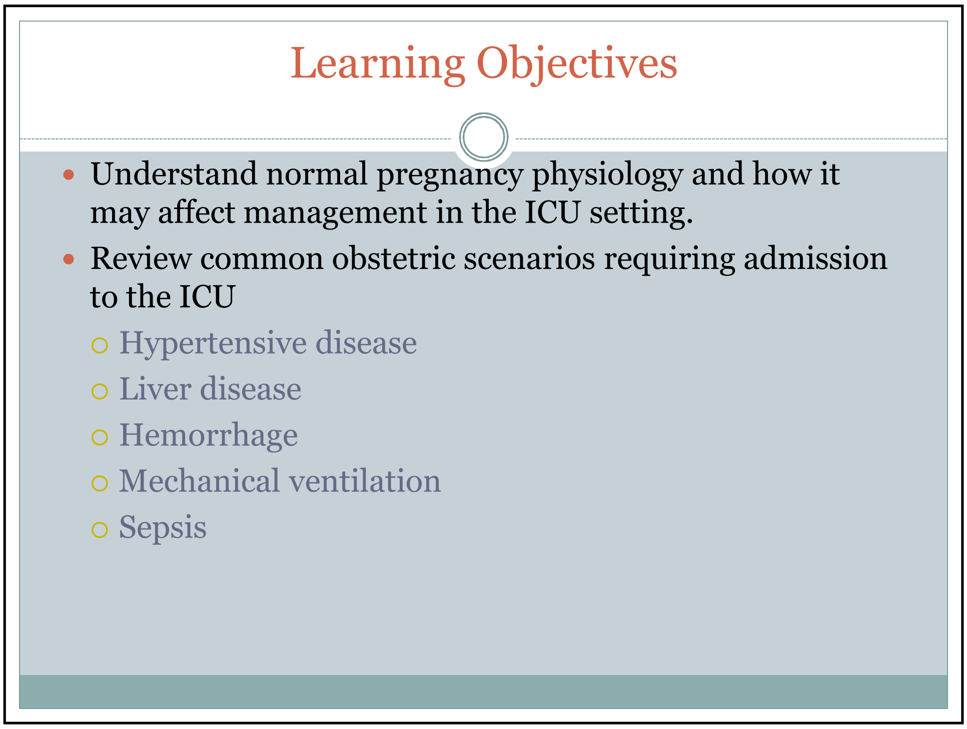
Ventilator Management in Pregnancy

- Minute ventilation adjusted to maintain PaCO2 between 30-32 mm Hg.
- PaCO2 less than 30 mm Hg should be avoided as significant respiratory alkalosis may decrease uterine blood flow.
- Maternal hypercapnia (PaCO2 >40mmHG) may cause fetal respiratory acidosis



Ventilator management in pregnancy

- Lung-protective strategy has not been formally tested in pregnant patients with ARDS **but is standard of care**
- Minor to moderate degrees of maternal hypoxemia are well tolerated in pregnancy
- Fetal PO_2 depends less on maternal PaO_2 than on maternal oxygen content (and associated oxygen delivery & extraction)
- Maternal hypercapnia may impair fetal CO_2 exchange and lower fetal pH
- FHR monitoring may be useful in determining maternal tidal volume & FIO_2



Learning Objectives

- Understand normal pregnancy physiology and how it may affect management in the ICU setting.
- Review common obstetric scenarios requiring admission to the ICU
  - Hypertensive disease
  - Liver disease
  - Hemorrhage
  - Mechanical ventilation
  - Sepsis

Sepsis: mortality

- In general ICU population 25-40%
- In OB ICU population
    - ~20% (case series, single-center)
    - 1-10% (population-based studies)
- Risk of death proportional to number of organ systems failing
- Septic deaths 50% multisystem organ failure, 50% refractory hypotension

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Maternal Sepsis Mortality and Morbidity During Hospitalization for Delivery: Temporal Trends and Independent Associations for Severe Sepsis

Melissa E. Bauer, DO,* Brian T. Bateman, MD, MSc,†‡§ Samuel T. Bauer, MD,||
Amy M. Shanks, MS, and Jill M. Mhyre, MD*

- 45 million hospitalizations
- 4158 cases severe sepsis
- Excludes ante- and postpartum
- Sepsis-related deaths doubled
    - 1998-2008

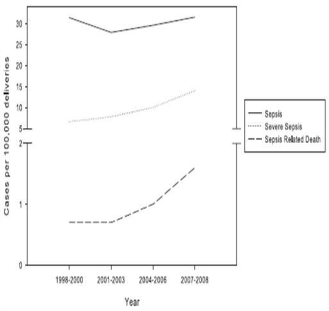


Figure 1. Temporal trends for maternal sepsis, severe sepsis, and sepsis-related death during hospitalization for delivery during 1998 to 2008 in the United States.

Anesthesia Analgesia 2013

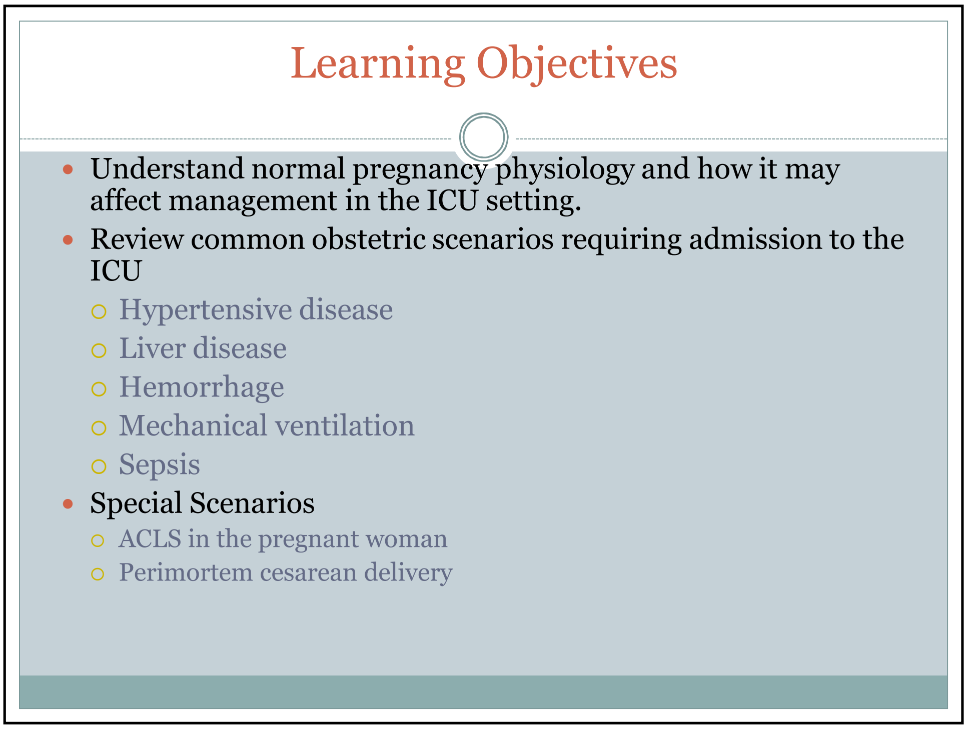
Sepsis

- Antenatal infections
  - Septic abortion
  - Chorioamnionitis
  - Complicated pyelonephritis
  - Pneumonia – Streptocoocus pneumoniae, influenza

- Postnatal infections
  - Endometritis – Group A streptococcus
  - Pelvic abscess
  - Septic pelvic thombophlebitis

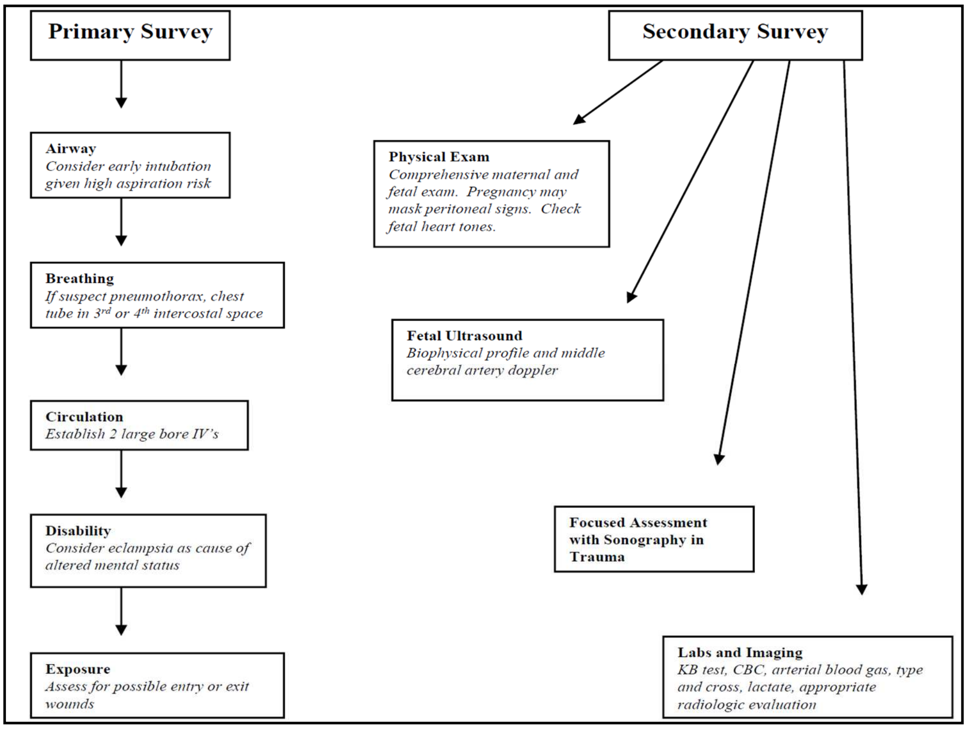
Sepsis Management

- Similar to non-pregnant patient
- Source control
  - Identify organism
  - Appropriate antibiotic use (avoid floxins, doxycycline, tetracycline)
- Pregnant women may be less responsive to volume due to hemodynamic changes (decrease SVR, leaky capillaries)
- Recommend judicious use of vasopressors
  - Norepinephrine
  - Phenylephrine



Learning Objectives

- Understand normal pregnancy physiology and how it may affect management in the ICU setting.
- Review common obstetric scenarios requiring admission to the ICU
  - Hypertensive disease
  - Liver disease
  - Hemorrhage
  - Mechanical ventilation
  - Sepsis
- Special Scenarios
  - ACLS in the pregnant woman
  - Perimortem cesarean delivery



Primary Survey

Airway
Consider early intubation given high aspiration risk

Breathing
If suspect pneumothorax, chest tube in 3rd or 4th intercostal space

Circulation
Establish 2 large bore IV's

Disability
Consider eclampsia as cause of altered mental status

Exposure
Assess for possible entry or exit wounds

Secondary Survey

Physical Exam
Comprehensive maternal and fetal exam. Pregnancy may mask peritoneal signs. Check fetal heart tones.

Fetal Ultrasound
Biophysical profile and middle cerebral artery doppler

Focused Assessment with Sonography in Trauma

Labs and Imaging
KB test, CBC, arterial blood gas, type and cross, lactate, appropriate radiologic evaluation

ACLS in Pregnancy

- Follow protocol as if the patient is not pregnant
  - After 20 weeks manual displacement of uterus (NOT LEFT TILT) is critical to effective circulation
- Medications may not circulate adequately if infused through lower extremity lines
  - Uterus compresses iliac veins
- Defibrillation should be performed with the same voltage as in non-pregnant patients
  - It is not harmful to the fetal cardiac rhythm

Peri-mortem Cesarean Section

- Initiate within 4 minutes of a malignant arrhythmia or maternal cardiac arrest
  - Manual uterine displacement is critical to effective ACLS
- Outcomes are optimal in neonates delivered w/in 5 minutes of maternal cardiac arrest.[16]
- If the pregnancy is beyond 25 weeks, there is a ~45% fetal & ~72% chance of maternal survival.[15]

Summary

- Despite advances in critical care maternal mortality and near-miss morbidity continues to increase
- Pregnancy is associated with significant physiologic and hemodynamic changes that may affect ICU management
- Hemorrhage, hypertensive disease, cardiac disease and respiratory failure most common source of ICU admissions
- Mortality prediction scores generally perform well but overestimate maternal mortality

Summary

- Uterine displacement one of the most useful methods to maintain and sometimes augment cardiac output in pregnancy
- Under normal conditions, pregnant patients can remain hemodynamically stable despite large volume losses
- There is a compromise of oxygen reserve in pregnant patients because of decreased FRC and increased O2 consumption
- Early transfer to tertiary setting with appropriate ICU care and multi-disciplinary team approach

Summary

- ACLS protocols do not deviate much from the standard

- In trauma/codes, keep the "4-5 rule" in mind for perimortem deliveries

- Pregnant women exist in a state of physiologic respiratory alkalosis.

Question #1
Progesterone is responsible for which physiologic alteration of pregnancy

A) INCREASED VOLUME EXPANSION
B) DECREASED FUNCTIONAL RESIDUAL CAPACITY
C) DECREASED CHEST WALL COMPLIANCE
D) INCREASED RESPIRATORY DRIVE
E) DECREASED TIDAL VOLUME

Progesterone acts to stimulate the respiratory center in the medulla and increases respiratory drive. This causes an increase in tidal volume by up to 40% which translates to an increased minute ventilation. The respiratory rate does not change significantly in pregnancy

Question #2

22 y/o G1 P0 being induced at 38 weeks. Pregnancy complicated by Class III lupus nephritis, elevated BPs (160-170/80-110) and new headache. Her baseline creatinine is 1.4 mg/dl and is elevated to 2.2mg/dl today. She is on a magnesium drip at 2 g/hr for seizure prophylaxis. On physical exam her deep tendon reflexes are absent and she is not breathing. The magnesium drip is turned off and you are called to see her. What can be given to treat this condition?

A) CALCIUM CARBONATE 1G PO IMMEDIATE RELEASE
B) CALCIUM CARBONATE 1G IV
C) CALCIUM GLUCONATE 1G IV
D) CALCIUM GLUCONATE 1G PO IMMEDIATE RELEASE
E) NOTHING NEEDS TO BE GIVEN, THESE ARE NORMAL SIDE EFFECTS

Magnesium toxicity can occur quickly in patients with impaired renal function.

-Therapeutic range=4.8 to 8.4 mg/dL (2.0 to 3.5 mmol/L)
-Loss of deep tendon reflexes= 9.6 to 12.0 mg/dL (4.0 to 5.0 mmol/L)
-Respiratory paralysis at 12.0 to 18.0 mg/dL (5 to 7.5 mmol/L)
-Cardiac arrest at 24 to 30 mg/dL (10 to 12.5 mmol/L).

Calcium gluconate 1 g IV over 5 to 10 minutes is given to counteract life-threatening symptoms of magnesium toxicity

Question #3

42 y/o G3 P0020 IVF pregnancy at 31 weeks with ARDS presumably from pyelonephritis. Her temperature is 101.2 F. She is on lung protective ventilation and her PCO2=58mmHg, PO2=148 mmHg on an FIO2 of 0.4. When she is placed on the fetal monitor, the fetal heart tracing shows repetitive late decelerations and no contractions. What is the most likely reason to explain this change in the fetal status?

A) MATERNAL HYPERCAPNEA
B) MATERNAL HYPERVENTILATION
C) MATERNAL FEVER
D) FETAL ADRENAL INSUFFICIENCY
E) UMBILICAL CORD COMPRESSION

Lung protective ventilation can be safely performed in pregnancy if one is mindful of the limitations on permissive hypercapnea in this population. Hypercapnea can result in reduced placental perfusion. There are no data the threshold PCO2 acceptable in pregnancy to prevent fetal acidosis. Uterine artery vasoconstriction occurs as maternal PCO2 approaches 60 mm Hg and can compromise placental perfusion. This can happen iatrogenically in lung-protective ventilation strategies, and careful avoidance of hypercapnea is paramount, particularly in viable pregnancies.

Question #4

19 y/o G1 P1 is now immediately post partum. Her medical history is significant for moderate persistent asthma. Her nurse called the OB in for excessive bleeding which was managed successfully with an IV medication. You are now being called to evaluate the patient for new onset wheezing and desaturation to 88%. What do you think precipitated this event?

A) USE OF METHYLERGONOVINE
B) PULMONARY EDEMA FROM IV FLUIDS
C) OXYTOCIN INFUSION
D) COINCIDENTAL ASTHMA EXACERBATION
E) USE OF CARBOPROST TROMETHAMINE

Bronchospasm is a known side effect of medications in the Prostoglandin F2α family like carboprost tromethamine. If given to a patient with an asthma history for the treatment of post partum hemorrhage, it can precipitate an asthma exacerbation. Methylergonovine should be avoided in hypertensive patients and those with a history of myocardial ischemia.

Question #5

You are called to a code on the labor and delivery floor. The primary OB suspects an amniotic fluid embolus. Which of the following statements is false regarding the management of this coding pregnant patient?

A) MEDICATIONS THROUGH FEMORAL LINES MAY NOT CIRCULATE
B) IF SHE NEEDS DEFIBRILLATION, IT SHOULD BE AT A LOWER VOLTAGE FOR FETAL SAFETY
C) HAND PLACEMENT FOR CHEST COMPRESSIONS SHOULD BE HIGHER THAN FOR NON-PREGNANT PATIENTS
D) COAGULOPATHY IS A KEY FEATURE OF THIS DISORDER
E) A PERIMORTEM CESAREAN SECTION SHOULD BEGIN BY 4 MINUTES INTO THE CODE FOR BETTER FETAL OUTCOMES

ACLS guidelines for cardiac arrest in pregnancy are well established and do not deviate much from non-pregnant patients. Defibrillation is not harmful to the fetus and should be performed with the same voltage as non-pregnant patients. Remember to keep chest compressions going for an extra 2 minutes before checking for return of spontaneous circulation.

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Acknowledgements

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- Corrina Oxford, MD
- Karen Davidson, MD

End of Life and Ethical Dilemmas

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Assistant Professor of Medicine, HMS
Associate Physician, BWH

Conflict of Interest

- No conflicts to report

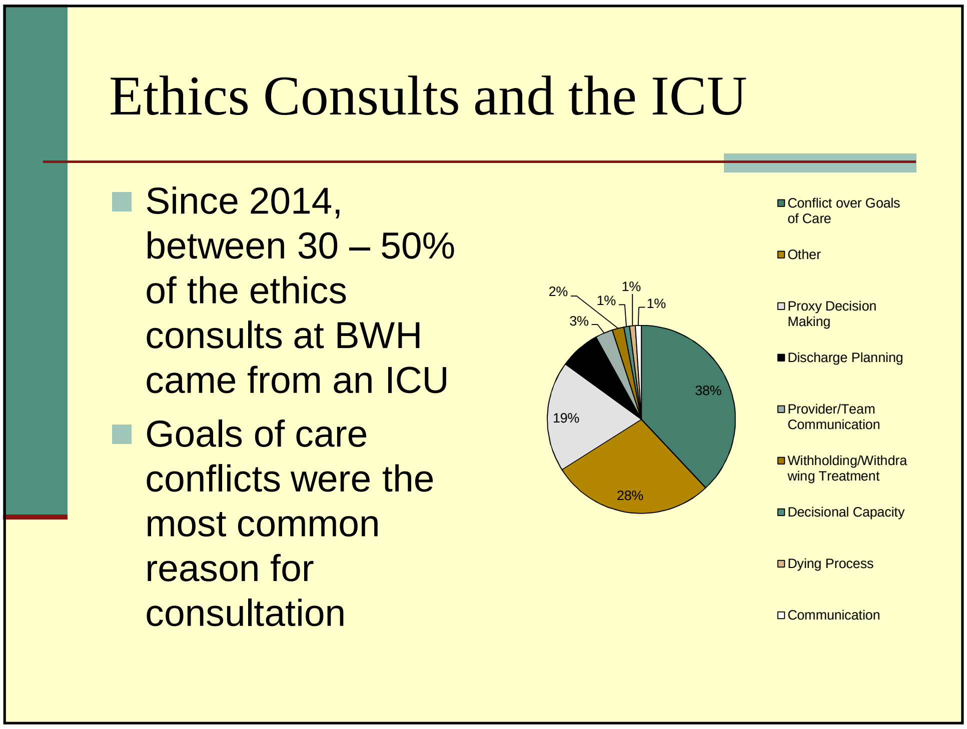
Outline

- Why end of life issues are important in the ICU
- Ethics – the basics
- Family impact
- Religion and culture
- Advance directives
- Decisional capacity/informed consent
- Potentially inappropriate care
- Other ethical dilemmas

End of Life Statistics

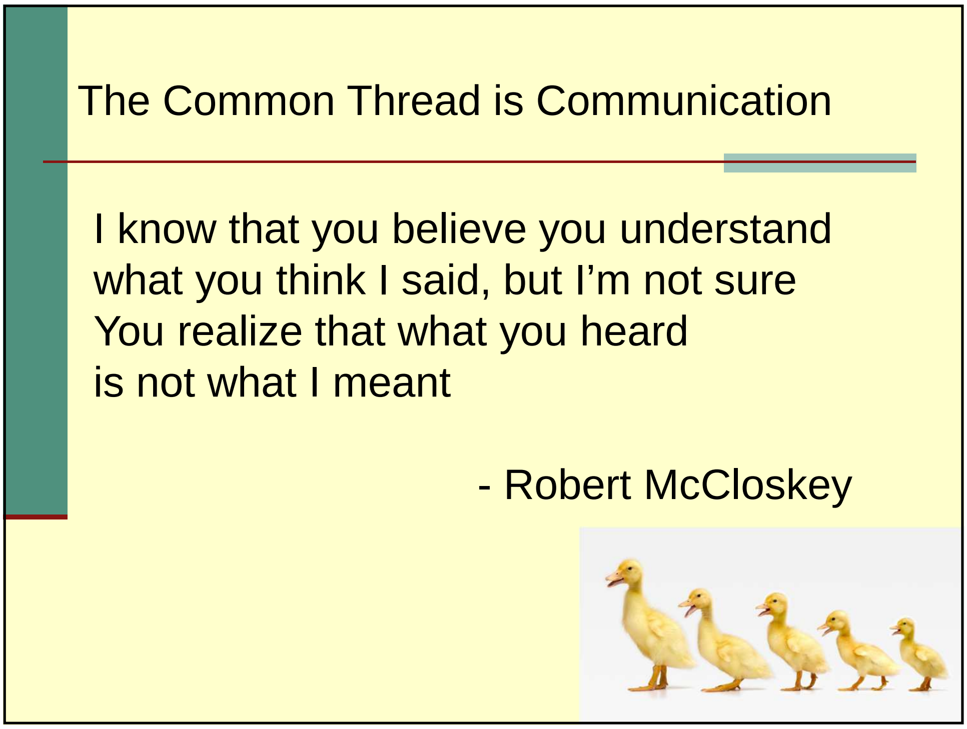
- ICU use at end of life
  - A survey of 1999 state-specific mortality statistics found 38% of all deaths occurred in a hospital
  - 22% of all deaths occurred in an ICU[1]
  - A study from 2010 showed 22% of Medicare patients with cancer died in an acute hospital, with 40% of patients having an ICU stay in the 180 days before death[2]
- Deaths in ICU
  - Cardiac arrest and “code blue”
  - More frequently, life-supportive technology removed

References: 1. Angus et al., Crit Care Med 2004
2. Bekelman et al., JAMA 2016



Ethics Consults and the ICU

- Since 2014, between 30 – 50% of the ethics consults at BWH came from an ICU
- Goals of care conflicts were the most common reason for consultation



The Common Thread is Communication

I know that you believe you understand
what you think I said, but I'm not sure
You realize that what you heard
is not what I meant

- Robert McCloskey

Ethics – the basic frameworks

- Normative ethics most commonly used
  - Autonomy – generally considered primary
  - Beneficence
  - Nonmaleficence
  - Social Justice
- Duty-based (deontological)
  - Consequences inform action, but are separate from determining right
  - Categorical imperative
- Ends-based (teleological)
  - The ends are critical components in determining right
  - Utilitarian: Greatest good for greatest number
  - Virtue: Right is what a perfectly virtuous person would do

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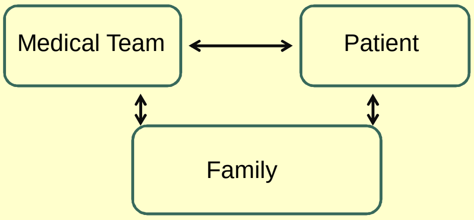
Relationships are at the center of any ICU ethical issues

Core Relationships in the ICU



ICU Ethical Issues Involve Patients and Their Families

- Critical illness impacts the family unit
  - PTSD – up to 69% of families of patients dying during their ICU admission[1]
  - Depression
- ICU management can ameliorate the impact on the family
  - Giving bad news
  - Importance of family meetings[2]
- Post-ICU follow-up

References:
1. A. Lautrette et al., NEJM 2007 vol 356, p469
2. J. Curtis et al., Crit Care Med 2001 vol 29, No. 2 (Suppl) P N26

Grief Management

- Response to receiving catastrophic news articulated by E. Kubler-Ross:
  - Denial/Shock
  - Anger
  - Bargaining
  - Grief/Depression
  - Acceptance
- Grief response is a non-linear process
  - ICU staff are limited in their ability to assist the process
  - May require time

Reference:

E. Kubler-Ross. On Death and Dying, Macmillan Publishing Company, 1969

Religion

- Major religions have very similar teachings about end of life therapy
  - No requirement for useless suffering, but is frequently cited as “reason” for pursuing burdensome care
  - Frequent requirement to seek and/or accept help
  - Can include specific directives about starting/stopping therapy
- Pastoral support can be invaluable to families
  - Prior relation with patient or family best
  - Extremely helpful if medical team talks directly with religious advisor

Culture

- Be aware, but be careful
  - Too great of an emphasis can result in stereotyping
  - Surprisingly similar views and concerns among families in US hospitals despite different ethnic backgrounds
  - International offices can be good resource
    - Medical translators can help with cross-cultural issues
- Have flexible approach to families to accommodate their beliefs about end of life and preferred decision making style
  - Shared decision making model is used most commonly
  - Doesn't work for all families or situations – a more directive approach is sometimes better

Advance Directives

- Allows for autonomy to be honored without patient's actual participation at time of decision
- Surrogate Decision Maker
- Advance Care Planning: Patient Self-Determination Act of 1990
  - Federal Statute
  - All states have legislation regarding Advance Directives

Surrogate Decision Maker

- Health Care Agent (HCA)/Durable POA for Healthcare
  - Legal, but simple, document (Healthcare Proxy)
  - HCA does not need to be related to patient
  - Copies with chart, HCA, Primary healthcare provider
  - Healthcare decisions during life (autopsy permission is permitted in some states)
  - Same prerogatives regarding health information as patient
  - Basis for decisions
    - Patient's clearly stated wishes
    - Substituted judgment
    - Best interests of the patient

Surrogate Decision Makers

- If no designated surrogates
  - Varies by state, but most frequently next of kin
    - 7 states do not have regulation about this, and Kansas has a regulation only about research consents[1]
    - MA, MN, MO,NE, NH, RI, VT
  - If no next of kin, synthetic judgment used
  - Some states require very clear prior statement of patient wishes and/or limit HCP authority[2]

References:

American Bar Association Commission on Law and Aging – www.abanet.org

Gillick, Advance Care Planning. NEJM 2004 vol. 350 p7-8

Advance Directives

- Advance Care Planning: Patient Self-Determination Act of 1990
  - American Bar Association website has updated information by state
  - Living Wills
    - Outlines preferences regarding treatment
    - Not binding in all states
  - Five Wishes
    - Non-profit organization “Aging with Dignity”
    - Written out instructions regarding decision makers, wishes regarding care
    - Meets state requirements in 42 states, can be appended to state form in 8
  - Gundersen Lutheran Medical Foundation “Respecting Choices®” – based in Wisconsin
    - Staged approach to integrating advance care planning into routine medical outpatient visits

Family Meetings in the ICU

- Before the meeting
  - Private area
  - Preparatory team meeting
- Early, frequent meetings help develop a consensus approach[1]
  - Clinical milestones
- Evidence-based approach: VALUE[2]
  - Value family statements
  - Acknowledge family emotions
  - Listen to the family
  - Understand the patient as a person
  - Elicit family questions

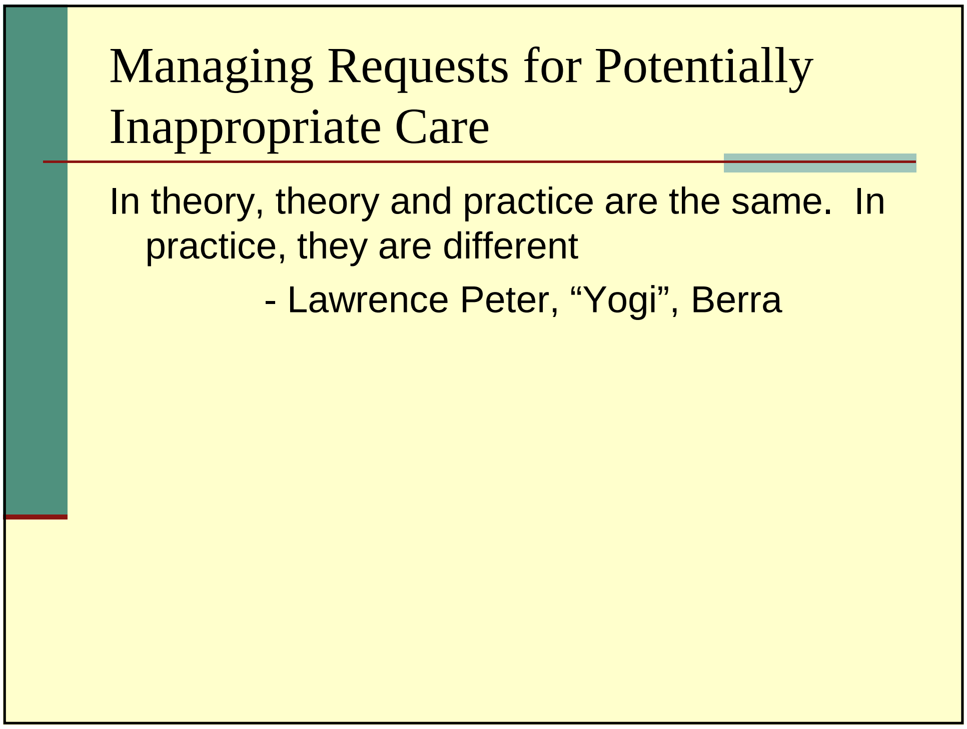
References:
CM Lilly et al., Am J Med 2000, vol 109 pp 469 - 475
JR Curtis and DB White, Chest 2008, vol 134 pp 835-843

Managing Discord

- A consensus plan among providers is vital
- Proactive, frequent family meetings with predetermined clinical milestones help to decrease discord
- If significant discord, get outside opinion and/or increase family support
  - Involve healthcare provider with long-term relationship
  - Ethics consult
  - Social services
  - Patient/family relations referral
  - Chaplaincy
- If intractable discord refer to hospital policy
  - Following policy does not prevent lawsuits, but does support the reasonableness of the healthcare provider's action

Communicate, Communicate, Communicate

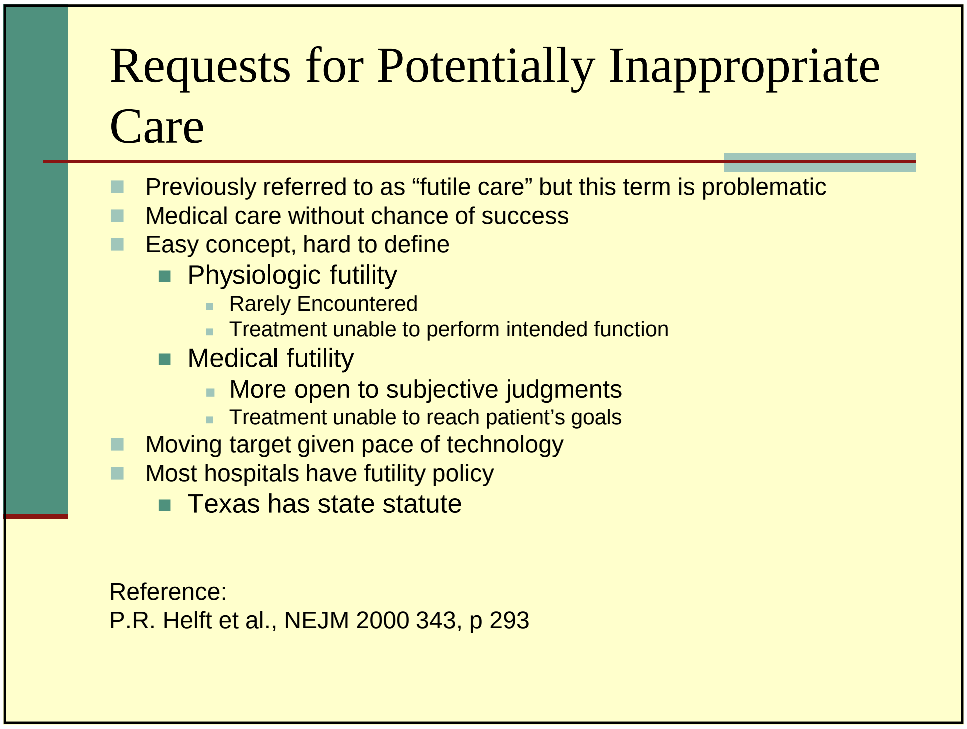
- Apparent discord frequently arises in setting of confusing or insufficient communication
- Identify agreed upon issues and goals first, then move to areas of disagreement
- Reframe issues as shared opportunity to work toward mutually held goals



Managing Requests for Potentially Inappropriate Care

In theory, theory and practice are the same. In practice, they are different

- Lawrence Peter, "Yogi", Berra



Requests for Potentially Inappropriate Care

- Previously referred to as "futile care" but this term is problematic
- Medical care without chance of success
- Easy concept, hard to define
  - Physiologic futility
    - Rarely Encountered
    - Treatment unable to perform intended function
  - Medical futility
    - More open to subjective judgments
    - Treatment unable to reach patient's goals
- Moving target given pace of technology
- Most hospitals have futility policy
  - Texas has state statute

Reference:
P.R. Helft et al., NEJM 2000 343, p 293

Comfort Care

- Occurs when the only goal of care is to treat symptoms
- Removal of life supporting therapies such as dialysis, VAD, mechanical ventilator
  - Ethically, removing a therapy is the same as not starting in the first place
  - Emotionally, it can be very different
- Double Effect
  - Accepts sedating side effects if intent is to relieve symptoms
  - Actually, use of benzodiazepines and opiates may not change duration of survival after removal of life supporting technology[1]

Reference:

J.D. Chan et al., Chest 2004, vol. 124 p286

End of Life and the Law

- Courts uphold right to refuse any care in landmark cases
  - Quinlan
  - Brody
  - Bartling
  - Cruzan
- Differentiates use of meds for symptom relief/palliative care and euthanasia: double effect
  - No right to euthanasia: Glucksberg and Vacco
- BUT – any "interested party" can initiate a legal review of any units practices
- Frequent source of anxiety among healthcare providers, but court actions have been very supportive of careful decision-making by healthcare professionals

References:

J.M. Luce, Crit Care Med 2001, vol 29, No2 (Suppl) pN42

A. Alpers, J Law Med Ethics 1998, vol 26 p308

Take-Home Points

- End of life issues are common in the ICU
- The ethical principles of autonomy, beneficence, nonmaleficence, and justice provide a framework to analyze difficult ethical issues arising around end of life issues
- Sensitive communication with a patient's family can lessen the distress associated with bereavement after a critical illness
- ICU physicians have a duty to provide palliative care to their dying patients

Decisional Capacity

- Distinct from "competency"
  - Competency is a specific legal term
- Capacity requires
  - Knowing available choices
  - Appreciating ramifications of available choices
  - A patient with capacity has the right to make a "wrong" decision
- Required for informed consent
- Difficult to assess in the critically ill – bedside tools available
  - CAM-ICU; Ely et al., Crit Care Med 2001
- A continuum instead of an absolute state
  - Capacity is decision-specific
  - Disorder of thinking doesn't necessarily preclude capacity

Research and Conflict of Interest

- Conflict of interest arises when a physician has dual roles
  - For example, an attending physician who has an actively enrolling clinical trial
- Usually managed by excluding the treating physician from recruiting patients into their own clinical trials
- The ethical issues raised by conflicts of interest:
  - Balance of risks and benefits
  - Informed consent can be problematic
  - Surrogate decision makers are limited from consenting for research in some states

Question 1

- The concept of “substituted judgment” is best described by
  - a. The medical team substituting for the patient by deciding what is in the patient’s best interests
  - b. The designated surrogate decision maker using their best understanding of how the patient would decide for themselves as the basis for decisions
  - c. The medical team substituting for the patient lacking a surrogate decision maker by using the “reasonable man” standard
  - d. The care instructions outlined in the “Five Wishes” or a living will
  - e. The court-appointed guardian using their understanding of the patient’s best interests as a basis for decisions

Question 1

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  b. **The designated surrogate decision maker using their best understanding of how the patient would decide for themselves as the basis for decisions**
  c. The medical team substituting for the patient lacking a surrogate decision maker by using the “reasonable man” standard
  d. The care instructions outlined in the “Five Wishes” or a living will
  e. The court-appointed guardian using their understanding of the patient’s best interests as a basis for decisions

Question 2

- A 70 year old man has just been admitted to your ICU with multisystem failure (shock, respiratory failure, and renal failure) due to pneumonia. His family consists of a wife, two daughters, and three sons. A close family friend is the patient’s healthcare agent. The patient’s healthcare agent visited the patient today, and told the patient’s nurse that the patient’s youngest son was not to be allowed to visit not receive any information about the patient. The patient’s wife and daughters were in earlier in the morning, but have left the hospital. They are expected to visit later in the day. Which of the following is correct?

a. The son may not visit nor receive information since the healthcare agent has refused permission for this.
b. No decision about the son’s ability to visit or receive information is possible at present, since the patient’s wife, as the next of kin, is the person who decides regarding whether her youngest son can visit and/or receive information about his father.
c. The son may not visit the patient since the healthcare agent has refused permission for this, but he can receive regular updates over the phone.
d. The patient’s son has a legal right to both visit and be informed about his father’s medical progress – the healthcare agent cannot infringe upon this.
e. The son may visit, but may not receive information about the patient since the healthcare agent has refused permission for this.

Question 2

- A 70 year old man has just been admitted to your ICU with multisystem failure (shock, respiratory failure, and renal failure) due to pneumonia. His family consists of a wife, two daughters, and three sons. A close family friend is the patient's healthcare agent. The patient's healthcare agent visited the patient today, and told the patient's nurse that the patient's youngest son was not to be allowed to visit not receive any information about the patient. The patient's wife and daughters were in earlier in the morning, but have left the hospital. They are expected to visit later in the day. Which of the following is correct?

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e. **The son may visit, but may not receive information about the patient since the healthcare agent has refused permission for this.**

Question 3

- Mrs. Williams is a 68 yr old woman with severe CHF (EF 10%), COPD (FEV-1 1.1L), and pneumonia. She has been on mechanical ventilation for 7 days. She does not have a health care proxy, but does have a living will indicating that she would not like support in the event of either a terminal disease or evidence of irreversible brain damage. Her family says she "has always been a fighter", and states that they believe she would want to continue therapy. However, the nurse caring for Mrs. Williams is uncomfortable with this plan. He points out that Mrs. Williams grimaces with mouth care and reaches for the endotracheal tube whenever her hands are not restrained. Which of the following would be the most appropriate course of action?

a. Call an ethics consult, since the patient's current status is clearly unacceptable to her, but her family is requesting continued mechanical ventilation

b. Arrange a family meeting to clarify the patient's values and goals, and establish whether the current treatment strategy is congruent with the patient's values

c. Adjust the patient's sedation so that she is more comfortable on the ventilator

d. All of the above

e. Choices B and C only

Question 3

- Mrs. Williams is a 68 yr old woman with severe CHF (EF 10%), COPD (FEV-1 1.1L), and pneumonia. She has been on mechanical ventilation for 7 days, and has not been able to communicate beyond intermittently nodding. She does not have a health care proxy, but does have a living will indicating that she would not like support in the event of either a terminal disease or evidence of irreversible brain damage. Her family says she "has always been a fighter", and states that they believe she would want to continue therapy. However, the nurse caring for Mrs. Williams is uncomfortable with this plan. He points out that Mrs. Williams grimaces with mouth care and reaches for the endotracheal tube whenever her hands are not restrained. Which of the following would be the most appropriate course of action?

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d. All of the above

e. **Choices B and C only**

Question 4

- Ms. Kirk is a 82 yr old woman who is on chronic mechanical ventilation and dialysis following an episode of sepsis. On morning rounds, it is reported that, during the night shift, the patient became tearful and wrote to her nurse that "not worth", and "home". This morning, the patient appears calm, but has a somewhat flattened affect. She interacts normally with the medical team, and participates as asked in all her therapy. The following day, the same report is given. What is the best course of action?

a. Start an antidepressant since the patient is having appropriate reactive depression.

b. Ask the covering moonlighting resident to check on the patient overnight.

c. Arrange a time to meet with the patient and her family to discuss her statements.

d. Ask the patient to clarify what she meant by her statements.

e. Start a low-dose atypical antipsychotic, such as haldol, in the evening, since the patient is having overnight agitation.

Question 4

- Ms. Kirk is a 82 yr old woman who is on chronic mechanical ventilation and dialysis following an episode of sepsis. On morning rounds, it is reported that, during the night shift, the patient became tearful and wrote to her nurse that "not worth", and "home". This morning, the patient appears calm, but has a somewhat flattened affect. She interacts normally with the medical team, and participates as asked in all her therapy. The following day, the same report is given. What is the best course of action?

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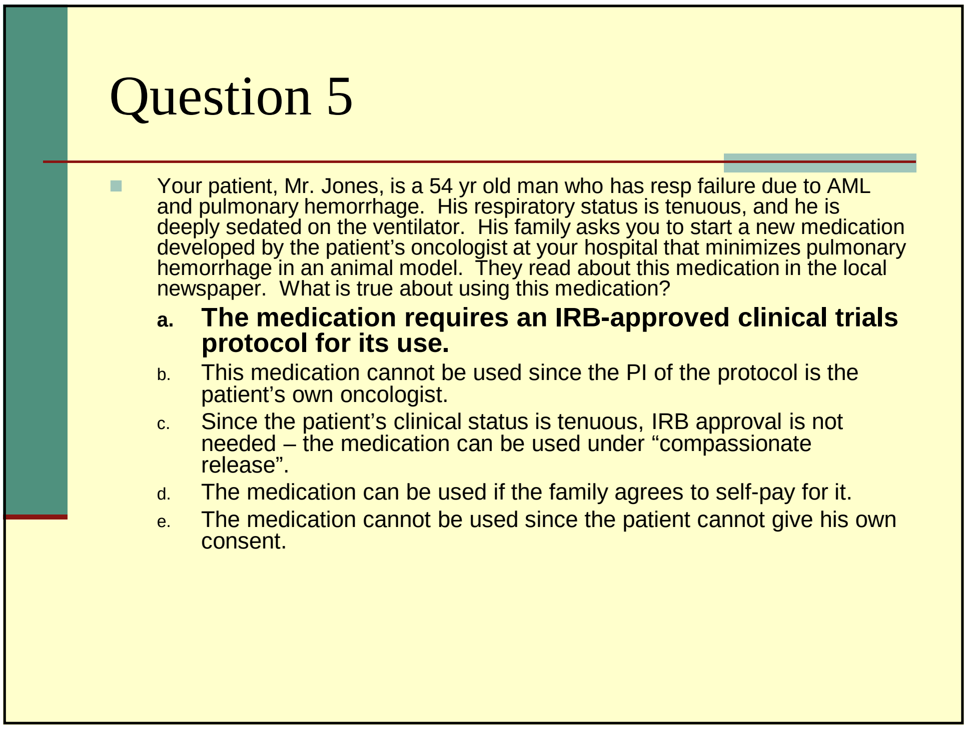
c. Arrange a time to meet with the patient and her family to discuss her statements.

d. **Ask the patient to clarify what she meant by her statements.**

e. Start a low-dose atypical antipsychotic, such as haldol, in the evening, since the patient is having overnight agitation.

Question 5

- Your patient, Mr. Jones, is a 54 yr old man who has resp failure due to AML and pulmonary hemorrhage. His respiratory status is tenuous, and he is deeply sedated on the ventilator. His family asks you to start a new medication developed by the patient's oncologist at your hospital that minimizes pulmonary hemorrhage in an animal model. They read about this medication in the local newspaper. What is true about using this medication?
  a. The medication requires an IRB-approved clinical trials protocol for its use.
  b. This medication cannot be used since the PI of the protocol is the patient's own oncologist.
  c. Since the patient's clinical status is tenuous, IRB approval is not needed – the medication can be used under "compassionate release".
  d. The medication can be used if the family agrees to self-pay for it.
  e. The medication cannot be used since the patient cannot give his own consent.



Question 5

- Your patient, Mr. Jones, is a 54 yr old man who has resp failure due to AML and pulmonary hemorrhage. His respiratory status is tenuous, and he is deeply sedated on the ventilator. His family asks you to start a new medication developed by the patient's oncologist at your hospital that minimizes pulmonary hemorrhage in an animal model. They read about this medication in the local newspaper. What is true about using this medication?
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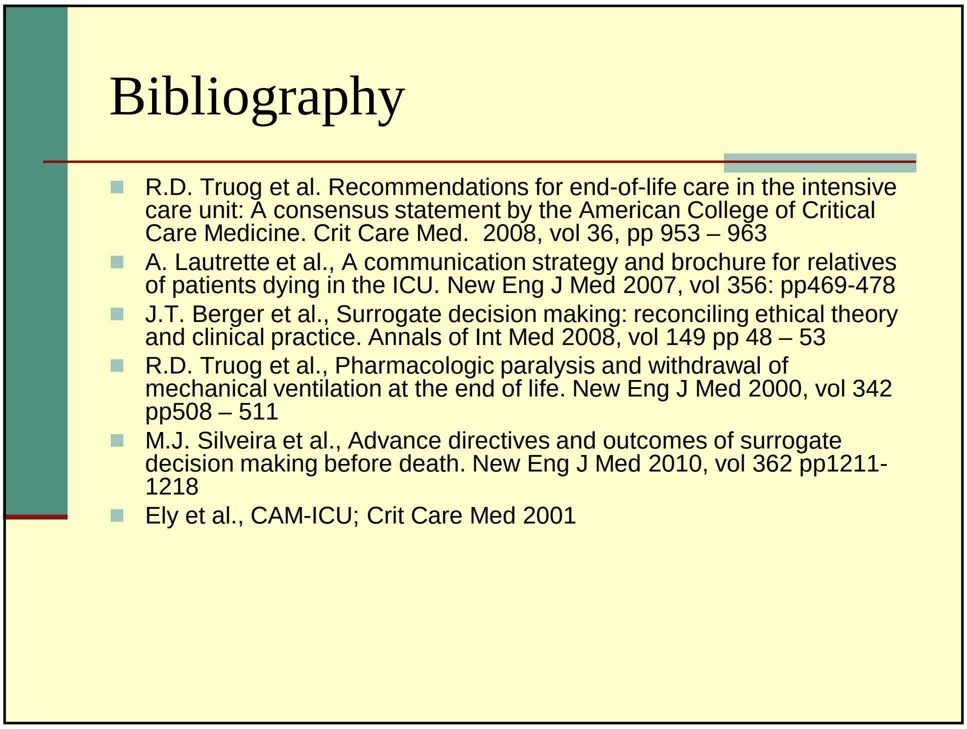

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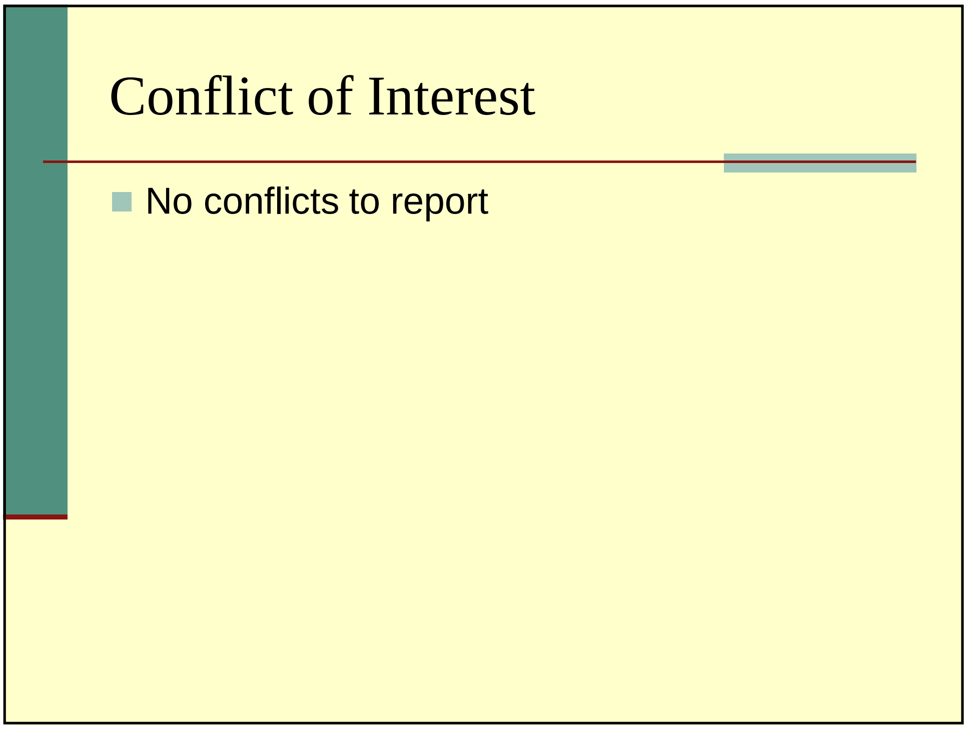
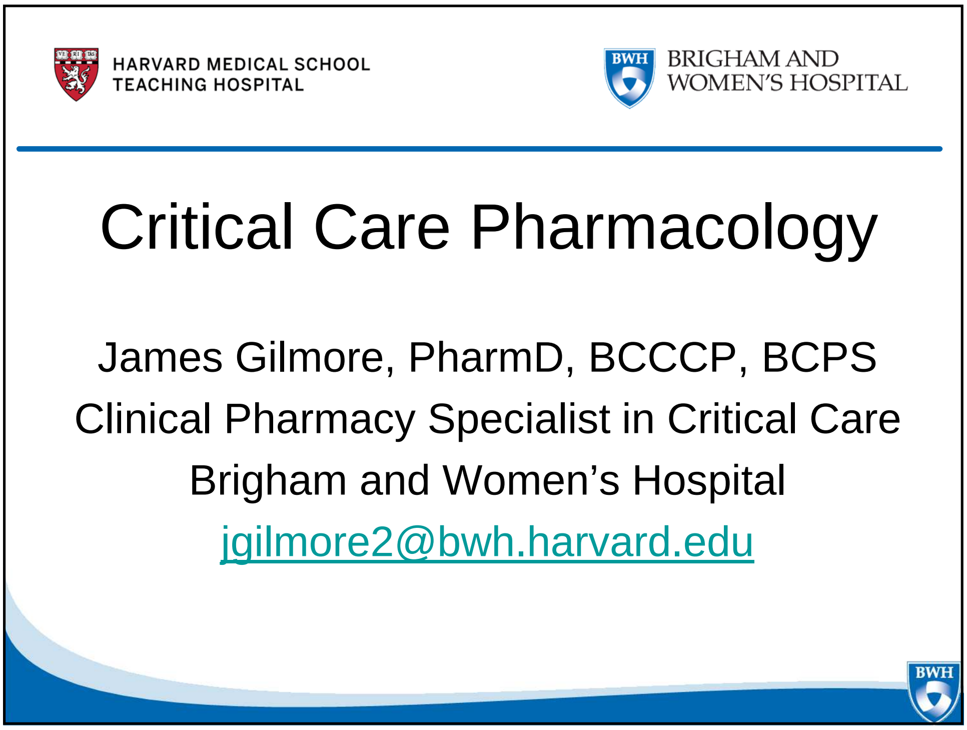
- Ely et al., CAM-ICU; Crit Care Med 2001



Conflict of Interest

- No conflicts to report



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

BRIGHAM AND
WOMEN'S HOSPITAL

Critical Care Pharmacology

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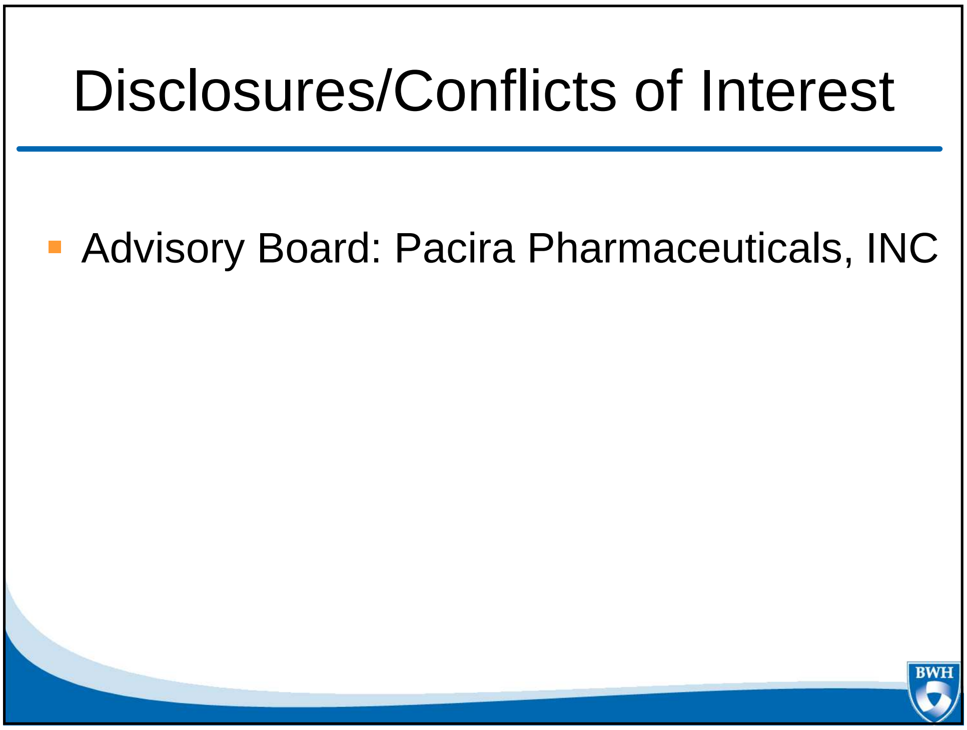

Disclosures/Conflicts of Interest

- Advisory Board: Pacira Pharmaceuticals, INC

Objectives

- Describe the principles of pharmacokinetic and pharmacodynamic
- Describe the changes in pharmacokinetics associated with critically ill patients and the impact on pharmacodynamics
- Describe ways to optimize pharmacokinetics and pharmacodynamics in critically ill patients
- To discuss alterations in pharmacotherapeutic response due to acute illness

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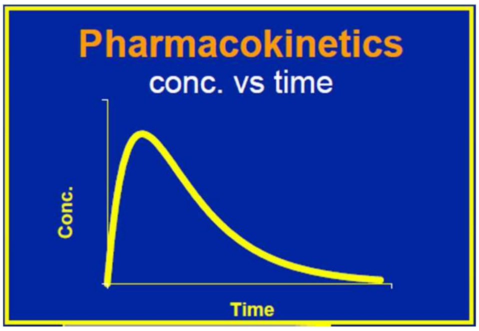
Pharmacokinetics (PK)

- Study of the time course of drug absorption, distribution, metabolism, and elimination
  - “What the body does to the drug”



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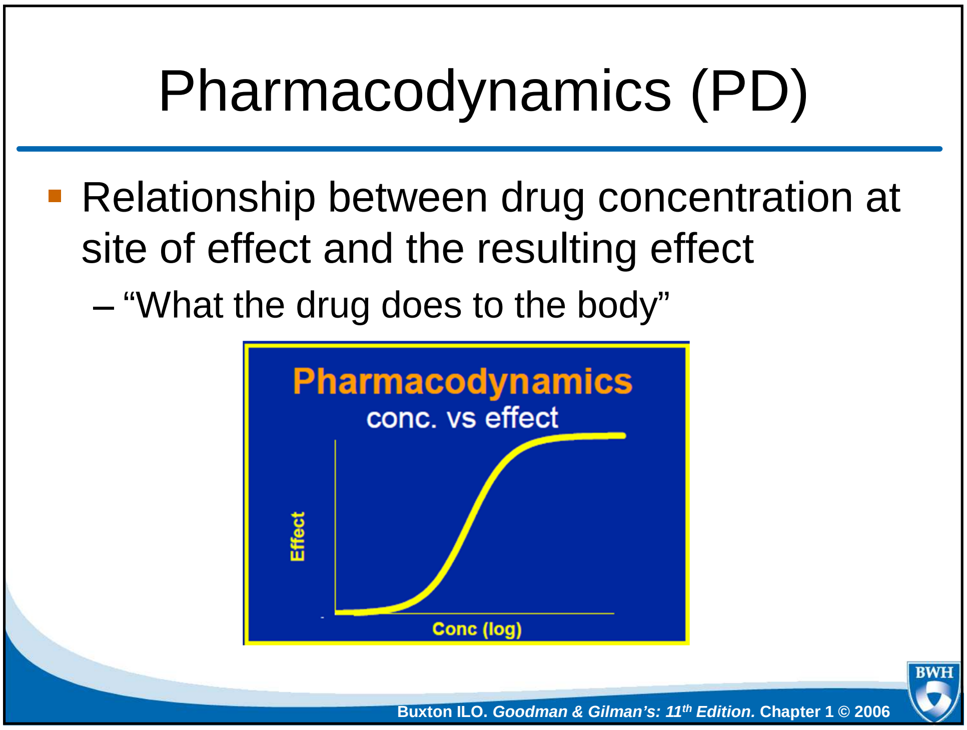

Pharmacodynamics (PD)

- Relationship between drug concentration at site of effect and the resulting effect
  - “What the drug does to the body”

Pharmacodynamics
conc. vs effect
Effect
Conc (log)
BWH

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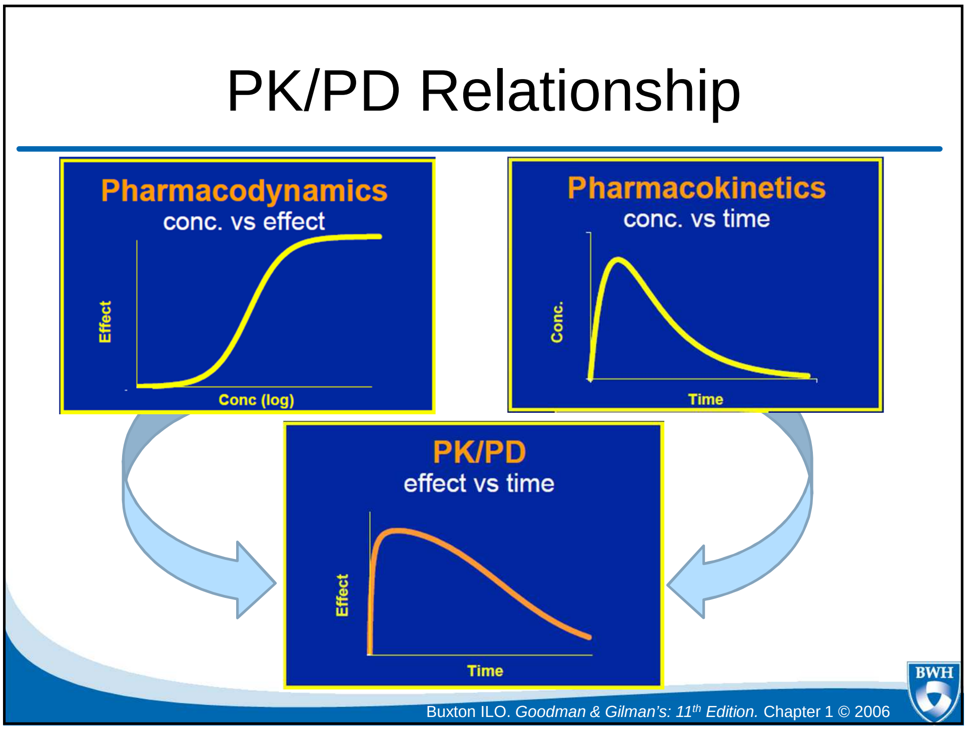

PK/PD Relationship

Pharmacodynamics
conc. vs effect
Effect
Conc (log)
Pharmacokinetics
conc. vs time
Conc.
Time
PK/PD
effect vs time
Effect
Time
BWH

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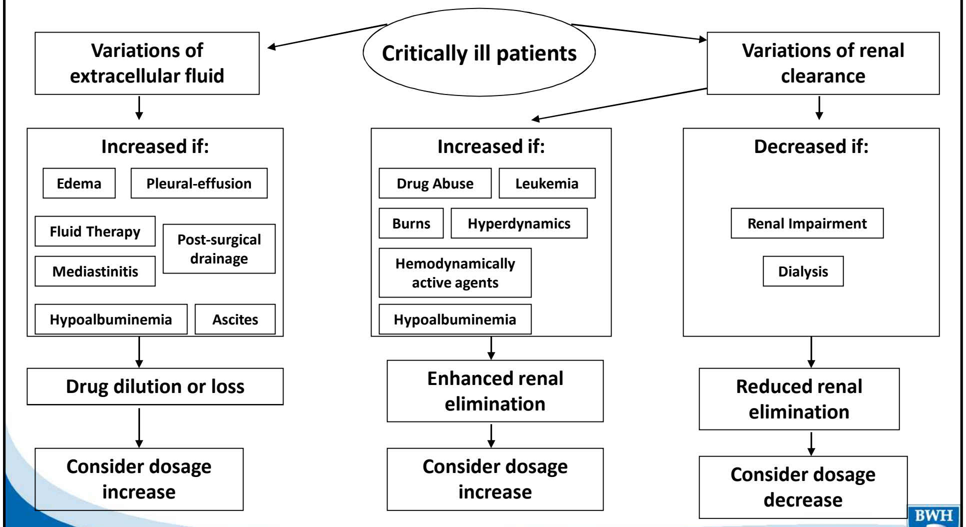
Pharmacokinetic Changes in Critical Illness



Critically ill patients

Variations of extracellular fluid

Increased if:

- Edema
- Pleural-effusion
- Fluid Therapy
- Post-surgical drainage
- Mediastinitis
- Hypoalbuminemia
- Ascites

Drug dilution or loss

Consider dosage increase

Variations of renal clearance

Increased if:

- Drug Abuse
- Leukemia
- Burns
- Hyperdynamics
- Hemodynamically active agents
- Hypoalbuminemia

Enhanced renal elimination

Consider dosage increase

Decreased if:

- Renal Impairment
- Dialysis

Reduced renal elimination

Consider dosage decrease

Pea F, Viale P. *Clin Infect Dis*. 2006; 42(12):1764-1771.

Absorption

Def: Extent of substance moving into systemic circulation from site of administration

- Bioavailability
  - *F* = fraction of administered drug absorbed
  - Dependant upon host physiological variables and specific drug properties
- Variables determining absorption:
  - Tissue Perfusion
  - Membrane
  - Drug properties
    - Vd (lipophilicity)
    - Molecular Size
    - Ionization

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Absorption: Routes of Administration

- IV (100%)
- PO
  - Fraction of dose absorbed (f_a)
    - Dissolution rate
    - Gastric motility
    - Solubility (TFs?)
  - Intestinal first pass extraction (E_G)
    - Or Pgp
  - Hepatic first pass extraction (E_h)
- SC
- IM
- TD
- SL
- PR
- PV
- NA
- INH

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Absorption in Sepsis

- Altered perfusion
  - Shunting
  - Hypovolemia
  - Vasoactive medications
- Intestinal atrophy
- Intestinal motility dysfunction
- pH changes
- Interactions with enteral nutrition

Boucher BA et al. *Crit Care Clin.* 2006; 22:255-271. Smith BS et al. *Chest.* 2012; 141(5):1237-1336.

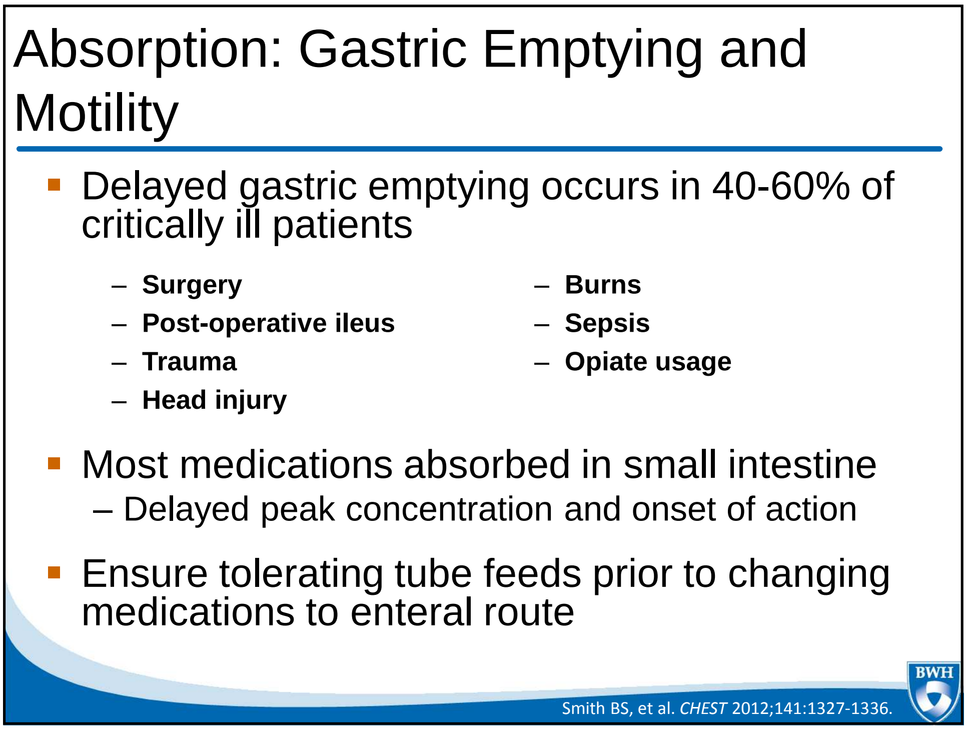
Which of the following is a common mechanism by which drug absorption is altered in critically ill patients?

1. Increased blood flow to the small intestines
2. Increased gastric emptying
3. Decreased gastric pH
4. Decreased blood flow to subcutaneous tissues

Absorption: Shock and Vasopressors

- Shock and vasopressor usage cause shunting of blood to vital organs
  - Brain, heart, lungs
- Blood flow to non-vital organs diminished
  - Gastrointestinal (GI) tract
  - Subcutaneous tissue
- Absorption diminished due to decreased blood flow
  - Enteral, transdermal, sublingual, intramuscular, subcutaneous

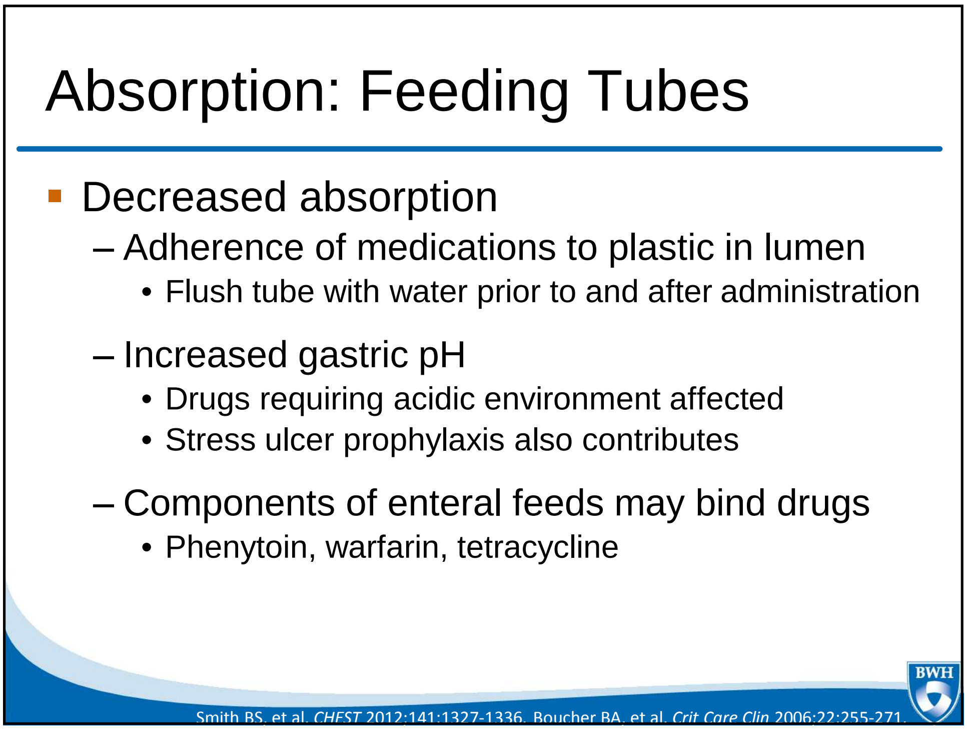
Smith BS, et al. *CHEST* 2012;141:1327-1336. Varghese JM, et al. *Crit Care Clin* 2011 Jan;27(1):19-34.



Absorption: Gastric Emptying and Motility

- Delayed gastric emptying occurs in 40-60% of critically ill patients
  - **Surgery**
  - **Post-operative ileus**
  - **Trauma**
  - **Head injury**
  - **Burns**
  - **Sepsis**
  - **Opiate usage**
- Most medications absorbed in small intestine
  - Delayed peak concentration and onset of action
- Ensure tolerating tube feeds prior to changing medications to enteral route

Smith BS, et al. *CHEST* 2012;141:1327-1336.

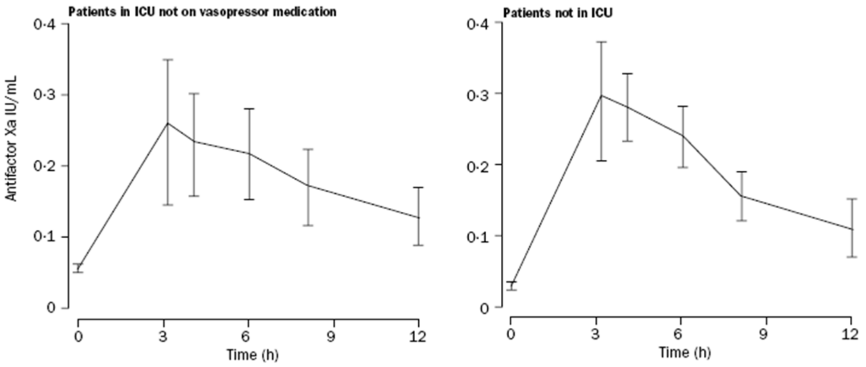


Absorption: Feeding Tubes

- Decreased absorption
  - Adherence of medications to plastic in lumen
    - Flush tube with water prior to and after administration
  - Increased gastric pH
    - Drugs requiring acidic environment affected
    - Stress ulcer prophylaxis also contributes
  - Components of enteral feeds may bind drugs
    - Phenytoin, warfarin, tetracycline

Smith BS, et al. *CHEST* 2012;141:1327-1336. Boucher BA, et al. *Crit Care Clin* 2006;22:255-271.

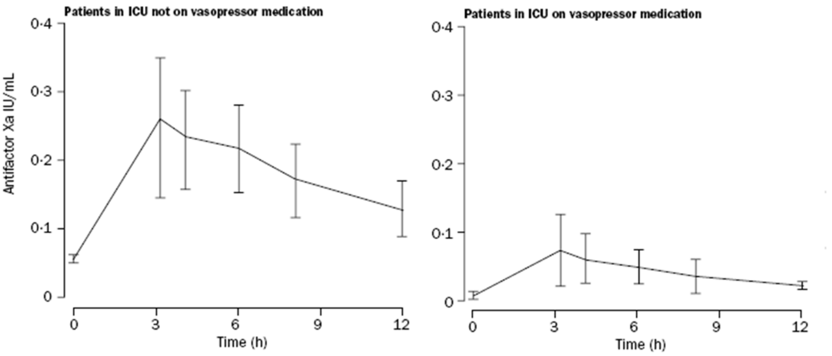
LMWH and Critical Illness



	Patients in ICU on vasopressors (n=15)	**Patients not in ICU (n=15)**
Arterial pressure (mean, 95% CI) (mm Hg)	64·3 (61·1–67·5)	87·3 (82·8–92·5)
APACHE II score (mean, 95% CI)	15·1 (13·2–16·9)	4·4 (3·8–5·2)

Dörffler-Melly J, et al. *Lancet.* 2002;359:849-50

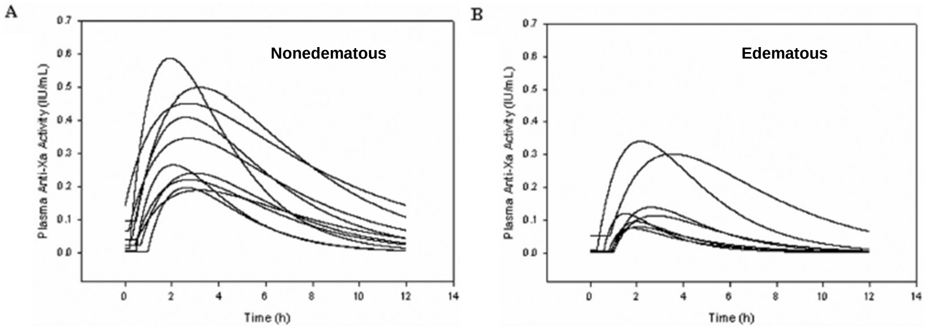
LMWH and Vasopressors



	Patients in ICU on vasopressors (n=15)	**Patients in ICU not on vasopressors (n=15)**
Vasopressor (number, %)*		
Dopamine (mean dose 17 μg/kg per min)	9 (60%)	0
Norepinephrine (mean dose 1·2 μg/kg per min)	6 (40%)	0
Phenylephrine (mean dose 4·5 μg/kg per min)	2 (13%)	0
Arterial pressure (mean, 95% CI) (mm Hg)	64·3 (61·1–67·5)	66·8 (62·2–70·4)
APACHE II score (mean, 95% CI)	15·1 (13·2–16·9)	14·2 (12·5–16·1)

Dörffler-Melly J, et al. *Lancet.* 2002;359:849-50

LMWH and Edema



Haas CE, et al. *Trauma*. 2005;59:1336-44

Oseltamavir Enteral Absorption

- 41 adult ICU patients with H1N1 influenza treated with oseltamivir
  - 75mg enterally twice daily achieved plasma levels comparable to those in the ambulatory setting

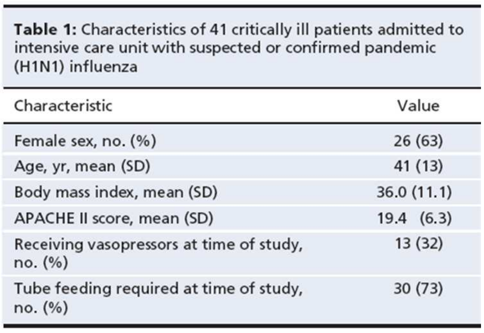
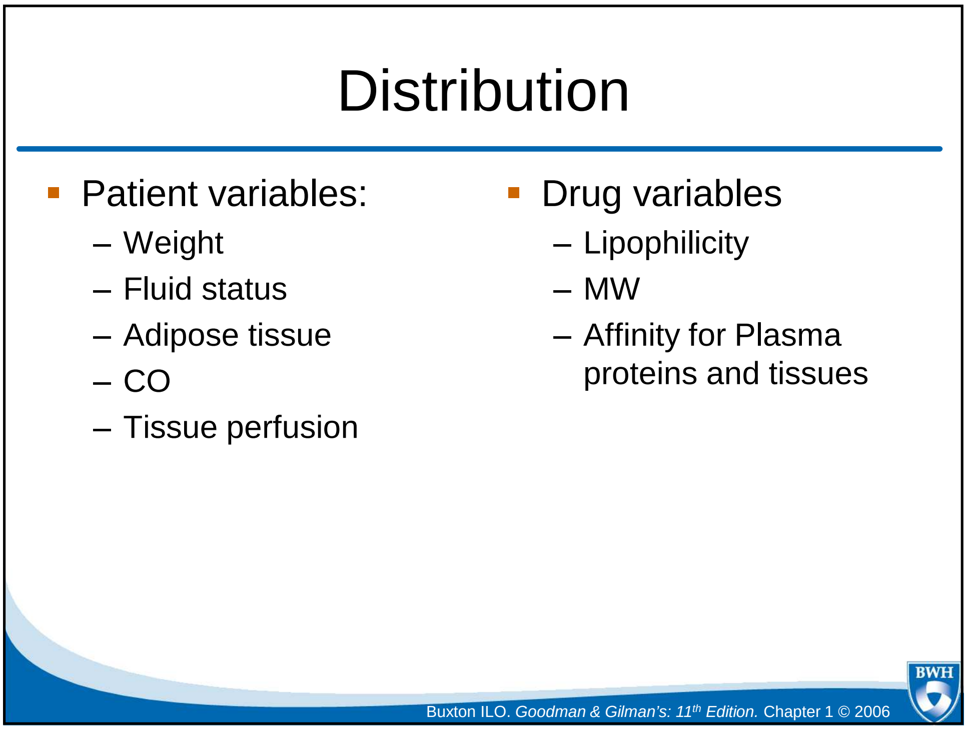


Table 1: Characteristics of 41 critically ill patients admitted to intensive care unit with suspected or confirmed pandemic (H1N1) influenza

Characteristic	Value
Female sex, no. (%)	26 (63)
Age, yr, mean (SD)	41 (13)
Body mass index, mean (SD)	36.0 (11.1)
APACHE II score, mean (SD)	19.4 (6.3)
Receiving vasopressors at time of study, no. (%)	13 (32)
Tube feeding required at time of study, no. (%)	30 (73)

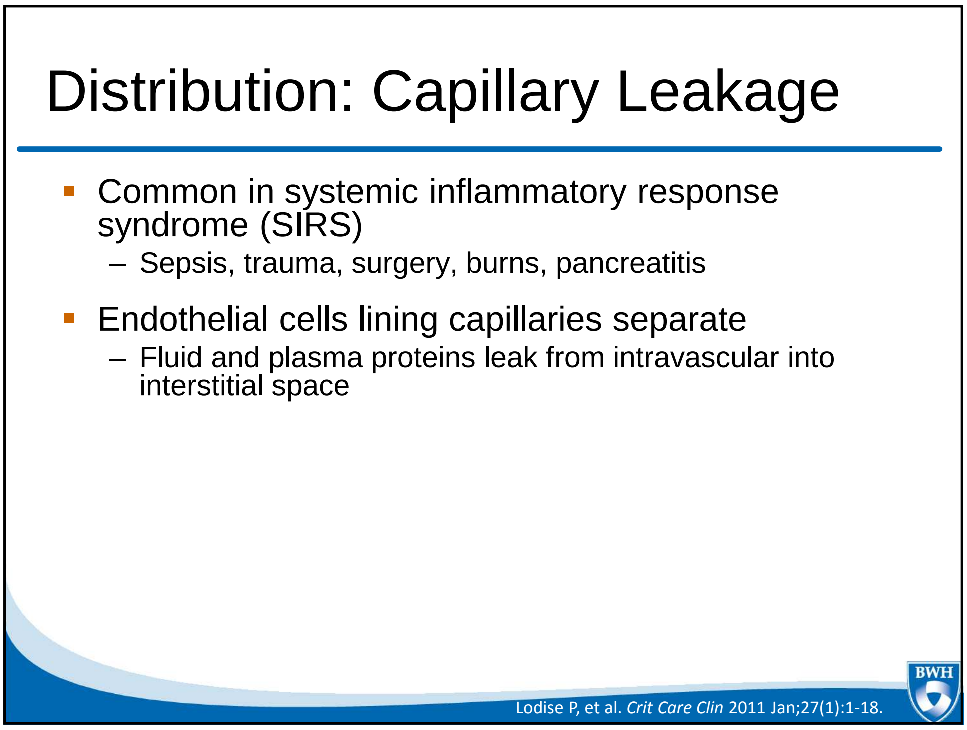
Ariano RE, et al. *CMAJ*. 2010;182:357-63



Distribution

- Patient variables:
  - Weight
  - Fluid status
  - Adipose tissue
  - CO
  - Tissue perfusion
- Drug variables
  - Lipophilicity
  - MW
  - Affinity for Plasma proteins and tissues

Buxton ILO. *Goodman & Gilman's: 11th Edition.* Chapter 1 © 2006



Distribution: Capillary Leakage

- Common in systemic inflammatory response syndrome (SIRS)
  - Sepsis, trauma, surgery, burns, pancreatitis
- Endothelial cells lining capillaries separate
  - Fluid and plasma proteins leak from intravascular into interstitial space

Lodise P, et al. *Crit Care Clin* 2011 Jan;27(1):1-18.

Distribution: Fluid Resuscitation

- Fluid resuscitation common in SIRS and shock
  - 30 mL/kg crystalloid in first 6 hours of severe sepsis
- Increases plasma volume
- Hydrophilic medications remain primarily in plasma water volume
  - Decreased serum concentrations
    - β-lactams
    - Aminoglycosides
    - Vancomycin

Smith BS, et al. *CHEST* 2012;141:1327-1336. Varghese JM, et al. *Crit Care Clin* 2011 Jan;27(1):19-34.

Distribution: Plasma Protein Binding

- Acidic drugs (e.g., phenytoin) bind to albumin
- Basic drugs (e.g., morphine) bind to α_1-acid glycoprotein (AAG)
- Hypoalbuminemia common in critical illness
  - Increased vascular permeability
  - Decreased hepatic production
    - Shift to acute phase reactants (e.g., AAG)
    - Malnutrition
  - Protein catabolism
- Unbound drug concentration mediates therapeutic drug effects

Smith BS, et al. *CHEST* 2012;141:1327-1336. Varghese JM, et al. *Crit Care Clin* 2011 Jan;27(1):19-34.

Distribution: Hypoalbuminemia

- Increased drug effect
  - Phenytoin: 90% bound to albumin
    - Goal total phenytoin concentration: 10-20 mg/L
    - Goal free phenytoin concentration: 1-2 mg/L
    - Increased proportion of free drug
      - Monitor **free** levels in critical illness
- Decreased drug effect
  - Ceftriaxone: 95% bound to albumin
    - 100% increased clearance
    - 90% greater V_D

Roberts JA, et al. *Crit Care Med* 2009;37:1-11.

Distribution: Tissue Perfusion

- Regional tissue hypoperfusion common in critical illness
  - Capillary leakage
  - Tissue edema
  - Microvascular failure
- Decreased delivery of hydrophilic medications by blood to capillary beds
  - Antibiotic penetration into tissues during septic shock decreases five to ten-fold

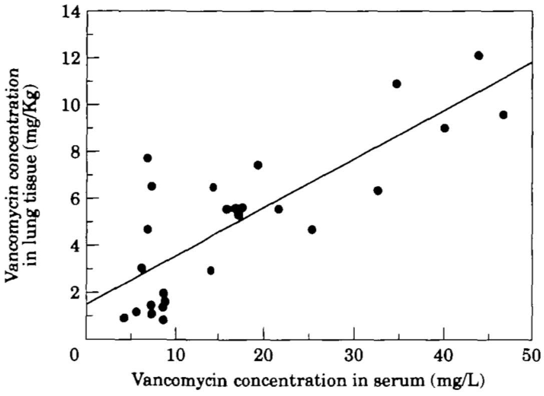
Smith BS, et al. *CHEST* 2012;141:1327-1336. Varghese JM, et al. *Crit Care Clin* 2011;27:19-34.

Changes in Critical Illness

- Increased volume of distribution
  - Shock states
  - Heart failure
  - Malnutrition – decreased protein binding
  - Prolonged exposure to lipophilic molecules
  - **Decrease in serum concentration**
- Decrease volume of distribution
  - Resolution of critical illness
  - Hypovolemia
  - Inflammation/fibrosis – reduction in tissue penetration
  - **Increase in serum concentration**

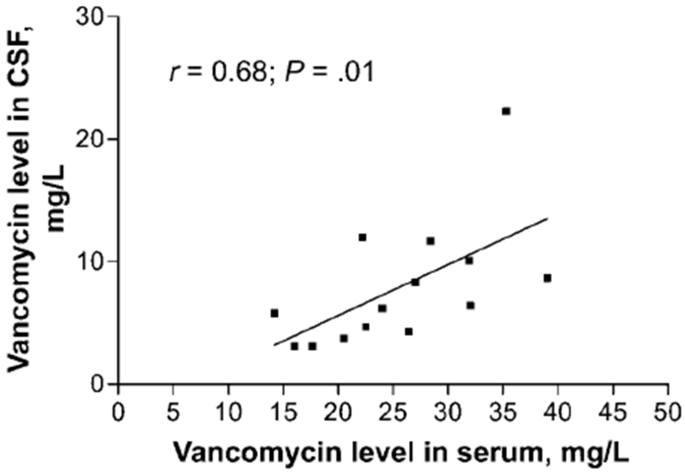
Boucher BA et al. *Crit Care Clin*. 2006; 22:255-271. Smith BS et al. *Chest*. 2012; 141(5):1237-1336. Buxton ILO. *Goodman & Gilman's: 11th Edition*. Chapter 1 © 2006

Penetration of Vancomycin into Human Lung Tissue



Scheetz MH, et al. *Pharmacotherapy*. 2006 Apr;26(4):539-50

Penetration of Vancomycin into Human CSF

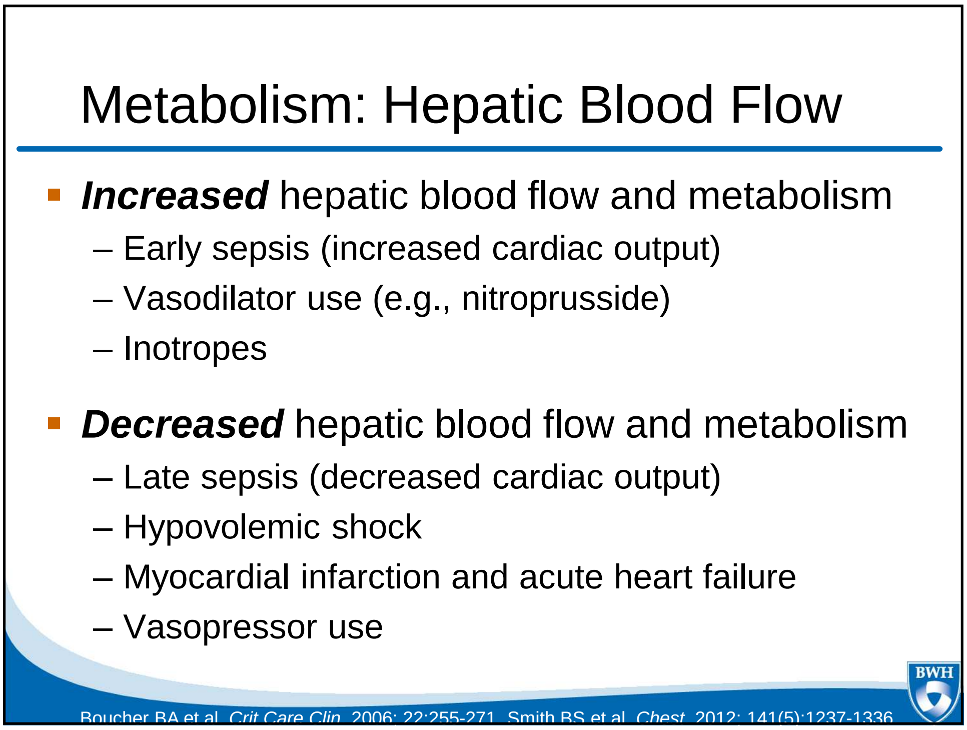


Richard JD, et al. *CID.* 2007;44:250-55

Metabolism

- Transformation of parent compounds into metabolites
  - Liver (primary site)
  - GI tract
  - Kidneys
  - Lungs
  - Brain
- Several alterations in critical illness
  - Hepatic enzyme activity
  - Protein binding
  - Hepatic blood flow

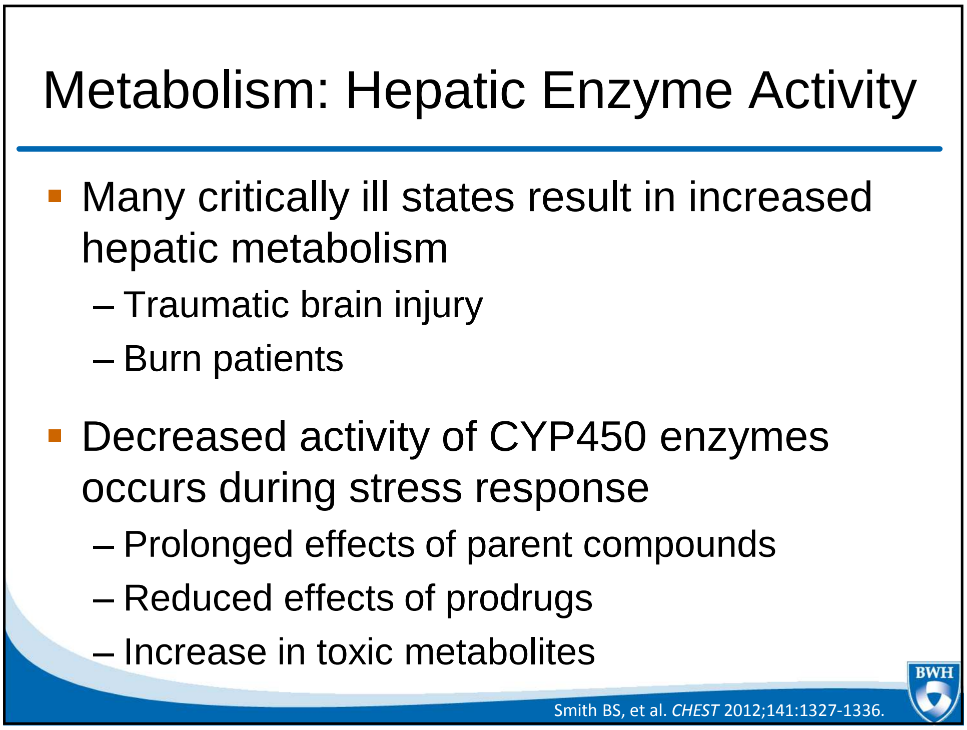
Smith BS, et al. *CHEST* 2012;141:1327-1336.



Metabolism: Hepatic Blood Flow

- ***Increased*** hepatic blood flow and metabolism
  - Early sepsis (increased cardiac output)
  - Vasodilator use (e.g., nitroprusside)
  - Inotropes
- ***Decreased*** hepatic blood flow and metabolism
  - Late sepsis (decreased cardiac output)
  - Hypovolemic shock
  - Myocardial infarction and acute heart failure
  - Vasopressor use

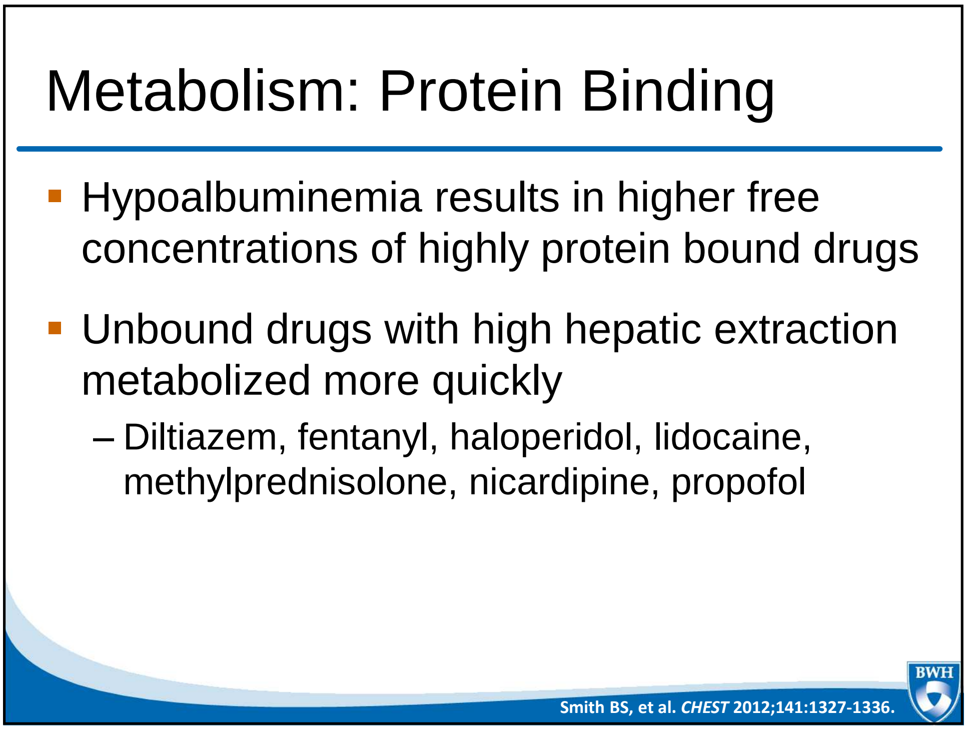
Boucher BA et al *Crit Care Clin* 2006; 22:255-271 Smith BS et al *Chest* 2012; 141(5):1237-1336



Metabolism: Hepatic Enzyme Activity

- Many critically ill states result in increased hepatic metabolism
  - Traumatic brain injury
  - Burn patients
- Decreased activity of CYP450 enzymes occurs during stress response
  - Prolonged effects of parent compounds
  - Reduced effects of prodrugs
  - Increase in toxic metabolites

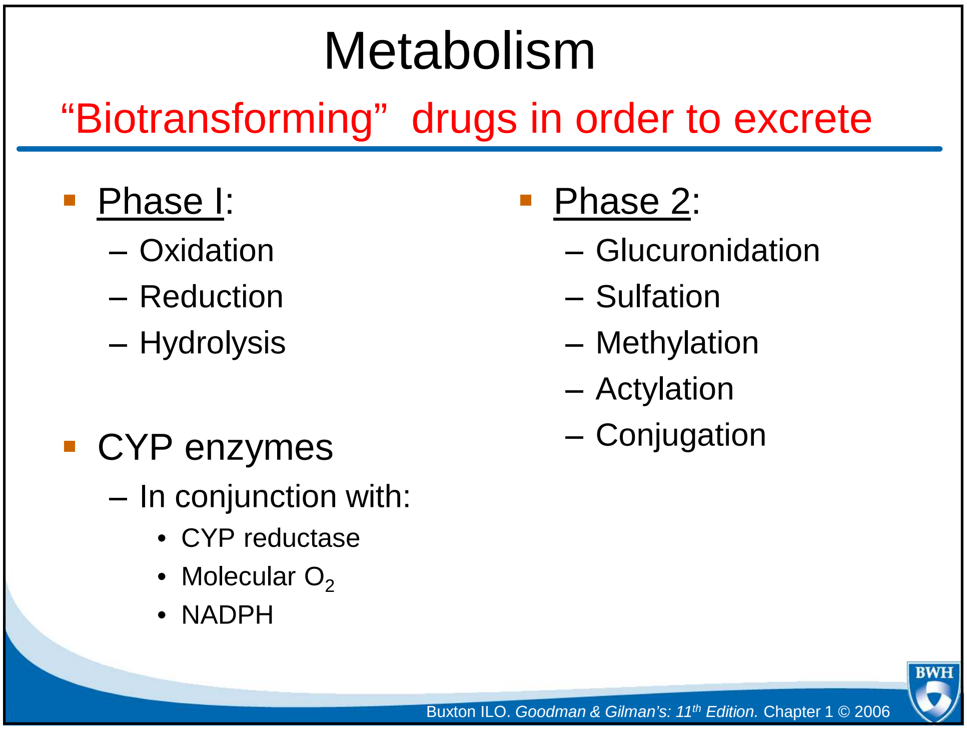
Smith BS, et al. *CHEST* 2012;141:1327-1336.



Metabolism: Protein Binding

- Hypoalbuminemia results in higher free concentrations of highly protein bound drugs
- Unbound drugs with high hepatic extraction metabolized more quickly
  - Diltiazem, fentanyl, haloperidol, lidocaine, methylprednisolone, nicardipine, propofol

Smith BS, et al. *CHEST* 2012;141:1327-1336.



Metabolism

“Biotransforming” drugs in order to excrete

- Phase I:
  - Oxidation
  - Reduction
  - Hydrolysis
- CYP enzymes
  - In conjunction with:
    - CYP reductase
    - Molecular O_2
    - NADPH
- Phase 2:
  - Glucuronidation
  - Sulfation
  - Methylation
  - Actylation
  - Conjugation

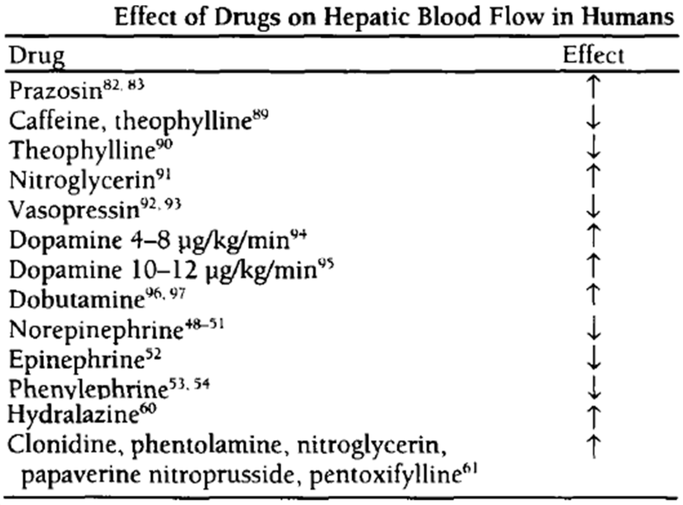
Buxton ILO. *Goodman & Gilman’s: 11th Edition.* Chapter 1 © 2006

CYP

- Located primarily in Liver
  - Can be affected by liver disease/failure
  - Also found in: small intestine, colon, kidney, brain, lungs, skin, nasal mucosa, heart, and eyes
- Contain genetic polymorphisms
  - Alter metabolism, increase metabolism, prodrugs
- Drug Interactions:
  - Inducers
  - Inhibitors
  - Substrates

Buxton ILO. *Goodman & Gilman's: 11th Edition.* Chapter 1 © 2006

Hepatic Blood Flow

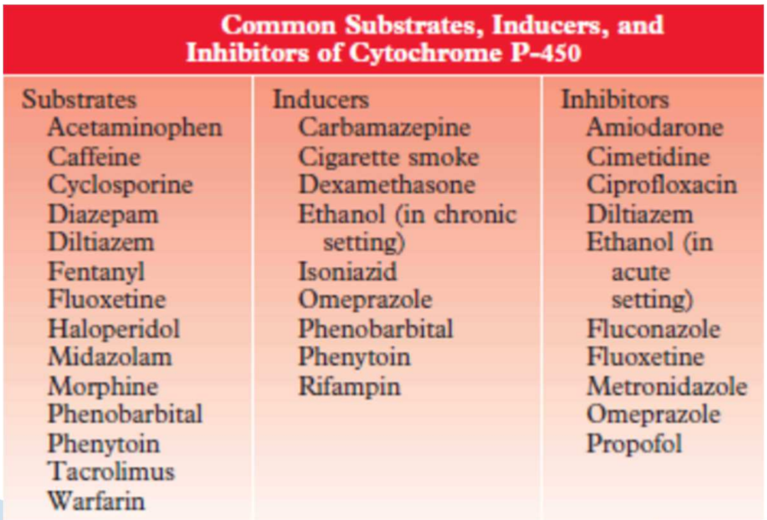


Effect of Drugs on Hepatic Blood Flow in Humans

Drug	Effect
Prazosin[82, 83]	↑
Caffeine, theophylline[89]	↓
Theophylline[90]	↓
Nitroglycerin[91]	↑
Vasopressin[92, 93]	↓
Dopamine 4–8 μg/kg/min[94]	↑
Dopamine 10–12 μg/kg/min[95]	↑
Dobutamine[96, 97]	↑
Norepinephrine[48–51]	↓
Epinephrine[52]	↓
Phenylephrine[53, 54]	↓
Hydralazine[60]	↑
Clonidine, phentolamine, nitroglycerin, papaverine nitroprusside, pentoxifylline[61]	↑

McKindley DS, et al. *Pharmacotherap.* 1998; 18:759-78

CYP-Dependent Medications



Common Substrates, Inducers, and Inhibitors of Cytochrome P-450

Substrates	Inducers	Inhibitors
Acetaminophen	Carbamazepine	Amiodarone
Caffeine	Cigarette smoke	Cimetidine
Cyclosporine	Dexamethasone	Ciprofloxacin
Diazepam	Ethanol (in chronic setting)	Diltiazem
Diltiazem	Isoniazid	Ethanol (in acute setting)
Fentanyl	Omeprazole	Fluconazole
Fluoxetine	Phenobarbital	Fluoxetine
Haloperidol	Phenytoin	Metronidazole
Midazolam	Rifampin	Omeprazole
Morphine		Propofol
Phenobarbital		
Phenytoin		
Tacrolimus		
Warfarin		

Elimination

- Half Life
  - – $T1/2 = 0.639/k_e$
  - – 97% of drug eliminated by 5 T1/2s
  - – ~4-5 T1/2 = steady state
- Clearance
  - – Volume of plasma, serum or blood cleared of the drug per unit of time
    - Kidney
    - Liver

Buxton ILO. *Goodman & Gilman's: 11th Edition.* Chapter 1 © 2006

Alterations in Liver Disease

- Pharmacokinetic
  - Decreased hepatocytes
  - Decrease in hepatic blood flow
  - Decreased albumin synthesis
  - Development of shunts
  - Impairment of renal function (HRS)
  - Altered drug absorption
  - Increased volume of distribution (Vd) for hydrophilic drugs
- Pharmacodynamic
  - Altered blood brain barrierpermeability
  - Altered receptor response

Verbeek RK. *Eur J Clin Pharmacol.* 2008; 64:1147-61.

Pharmacokinetic Changes in Cirrhosis

- Plasma protein binding
  - Reduced, but can have variable effect on drug half-life
    - Reduced half-life if patient maintains hepatic enzyme capacity
    - Increased half-life if metabolic capacity is reduced
  - Binding changes relevant for highly bound (>80%) drugs
- Metabolic capacity – Phase I often affected to a greater extent than Phase II

Krajembuhl S, Reichen J. *Medicine.* 2002; 30:24-7.

Assessing Liver Function

- Current classification schemes (Child-Pugh/ Model for End-Stage Liver Disease [MELD]) lack sufficient sensitivity to quantify liver metabolic capacity
- Child-Pugh classification used by manufacturers when studying PK parameters
- The following can be considered when approximating hepatic function:
  - Presence of cirrhosis
  - Synthetic function: INR/Albumin
  - Encephalopathy

Dose Adjustments in Cirrhosis

- No single approach is available
- High hepatic extraction drugs:
  - Loading dose needs to be reduced
  - Maintenance dose needs to be reduced
- Low hepatic extraction drugs:
  - Loading dose does not need to be reduced
  - Maintenance dose needs to be reduced
  - Degree of reduction based *grossly* on Child-Pugh classification
    - 8-9: Reduce dose by 25%
    - $\geq$10: Reduce dose by 50%
- Measure plasma drug levels when possible

Kraiembuhl S, Reichen J. *Medicine*. 2002;24-7. Lewis JH, Stine JG. *Aliment Pharmacol Ther*. 2013; 37:1132-56.

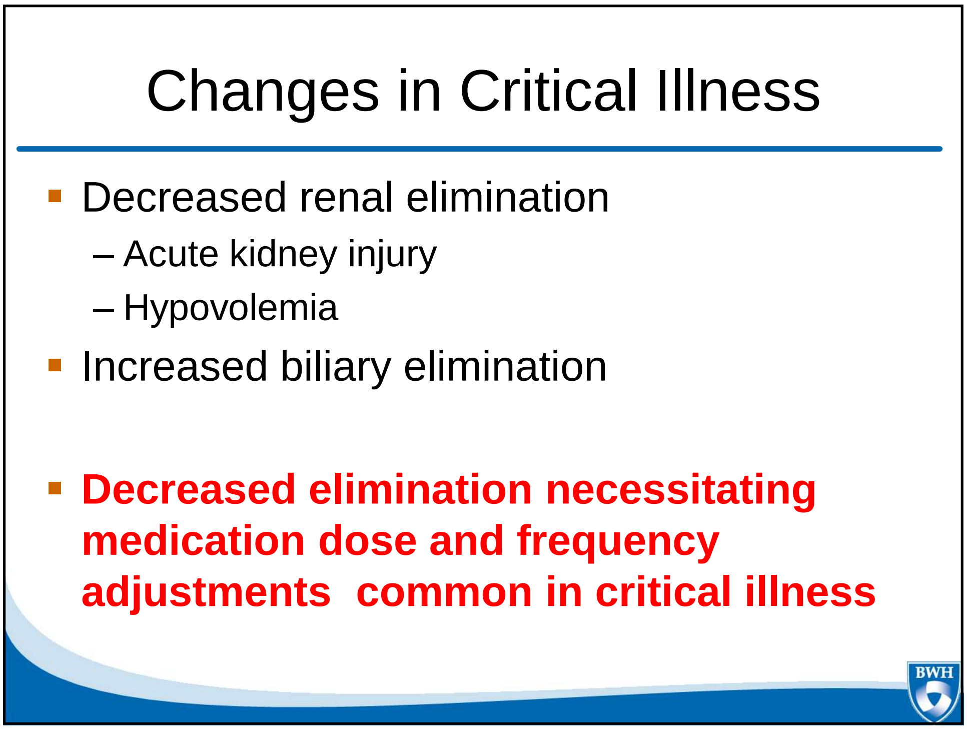
Metabolism in Sepsis

- Hepatic blood flow
  - Increased
    - Hyperdynamic sepsis phase (↑CO)
  - Decreased
    - Late sepsis
    - Shock (hypovolemic, hemorrhagic)
- Protein binding
  - Increased AAG
  - Decreased albumin
- Hepatic clearance

Boucher BA et al. *Crit Care Clin.* 2006; 22:255-271. Smith BS et al. *Chest.* 2012; 141(5):1237-1336.

Renal Elimination

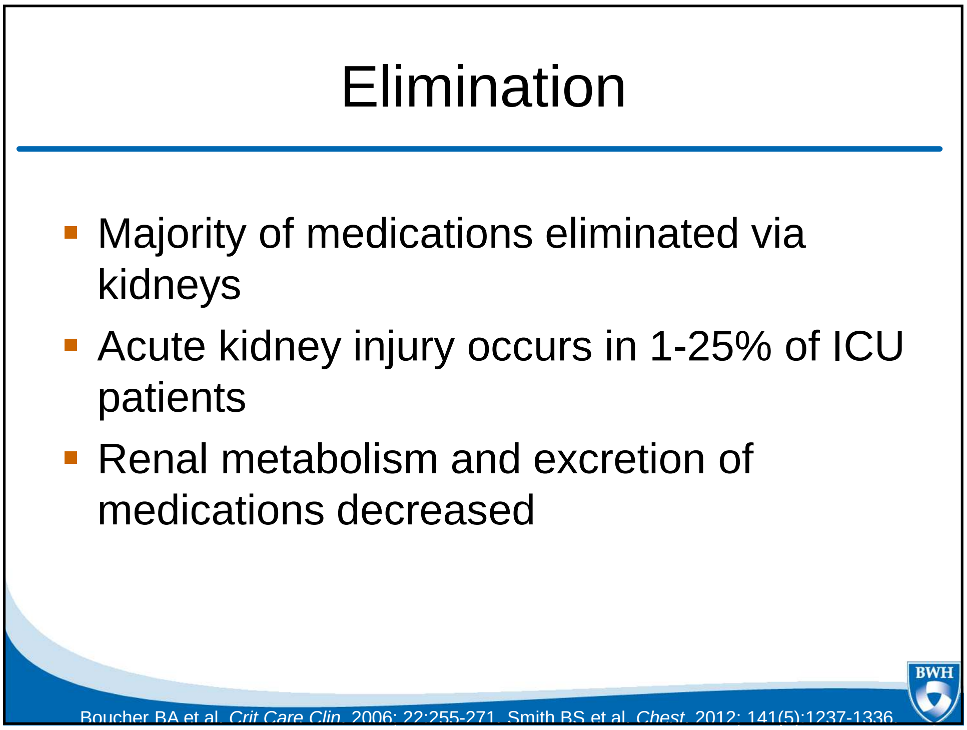
- GFR
- CrCL (mL/min) = rate of urinary creatinine excretion/serum creatinine concentration
- CrCL (mL/min) = (UCrV × 100)/(SCr × 1,440)
- CrCL = [(140 − age) × IBW]/(72 × SCr)
  - Multiply by 0.85 for females
- SCr….



Changes in Critical Illness

- Decreased renal elimination
  - Acute kidney injury
  - Hypovolemia
- Increased biliary elimination

- **Decreased elimination necessitating medication dose and frequency adjustments common in critical illness**

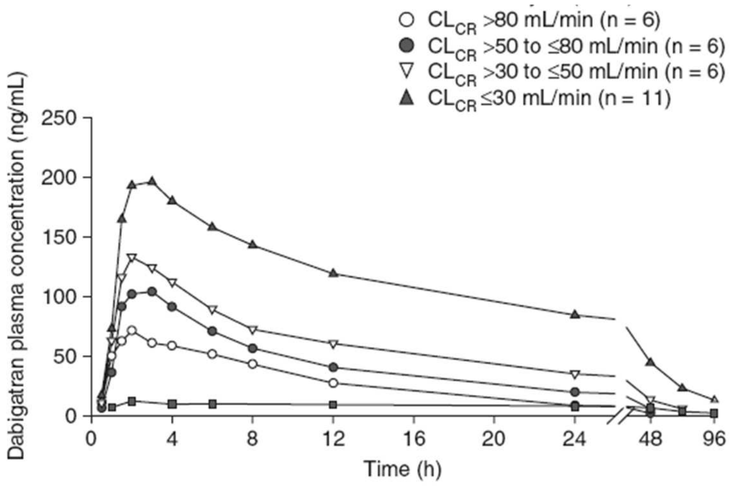


Elimination

- Majority of medications eliminated via kidneys
- Acute kidney injury occurs in 1-25% of ICU patients
- Renal metabolism and excretion of medications decreased

Boucher BA et al. *Crit Care Clin*. 2006; 22:255-271. Smith BS et al. *Chest*. 2012; 141(5):1237-1336.

Renal Clearance and Dabigatran



Stangier J, et al. *Clin Pharmacokinet*. 2010;49:259-68

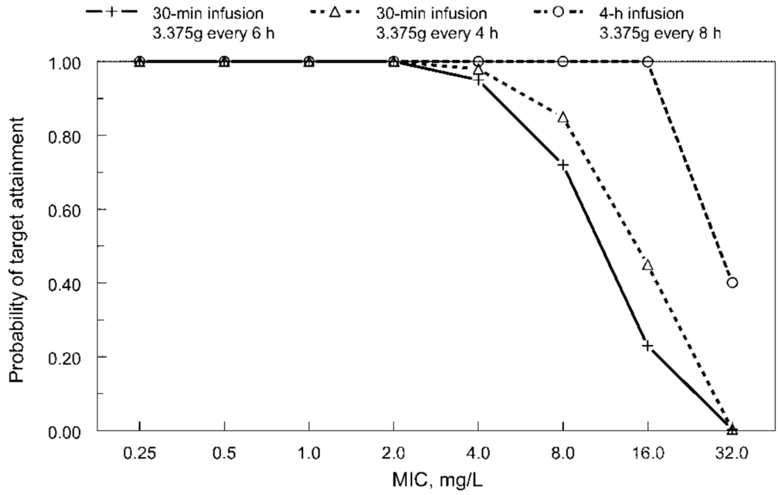
Optimizing PK/PD in the Critical Illness

- Prolonged infusions of time dependent antimicrobials
- Intravenous insulin
- Protocols for sedation and spontaneous awakening trials

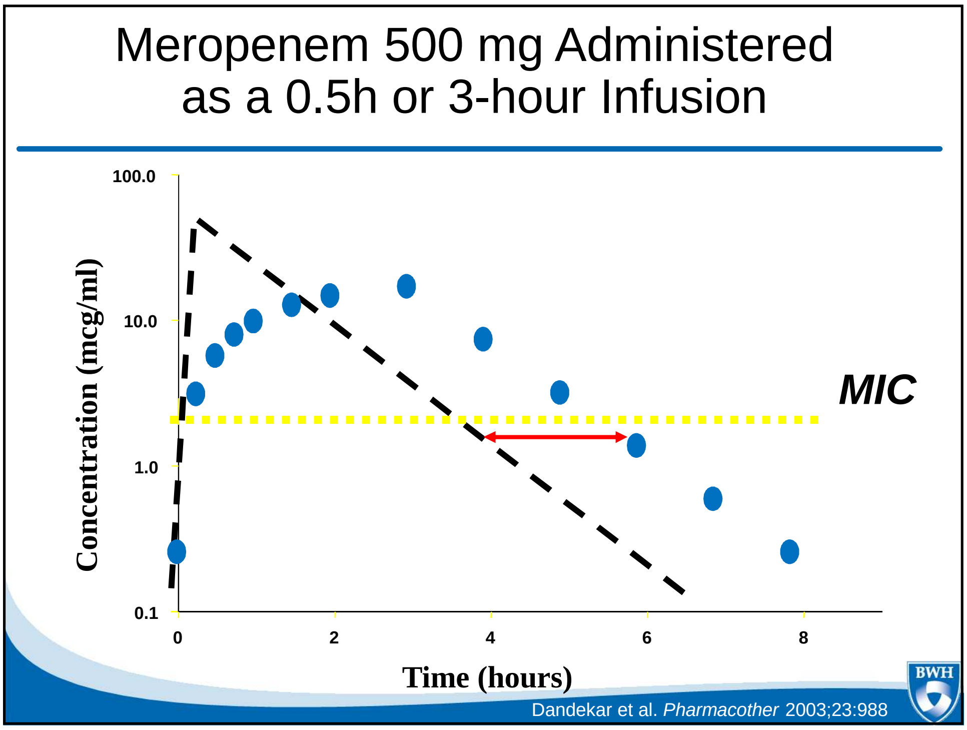
Time Dependent

- Pharmacodynamic Goal: Optimize *f*T>MIC
- [drug] > 4-5x the MIC = time dependent bactericidal activity
  - Bacterial killing seldom affected by increasing drug concentration
  - Extent of bacterial killing is 1º dependent on duration of exposure above MIC
- Beta lactams (PCNs, CPNs, monobactams, carbapenems) glycopeptides, macrolides, clinda, TCYs, and oxazolidinones

Probability of Target Attainment

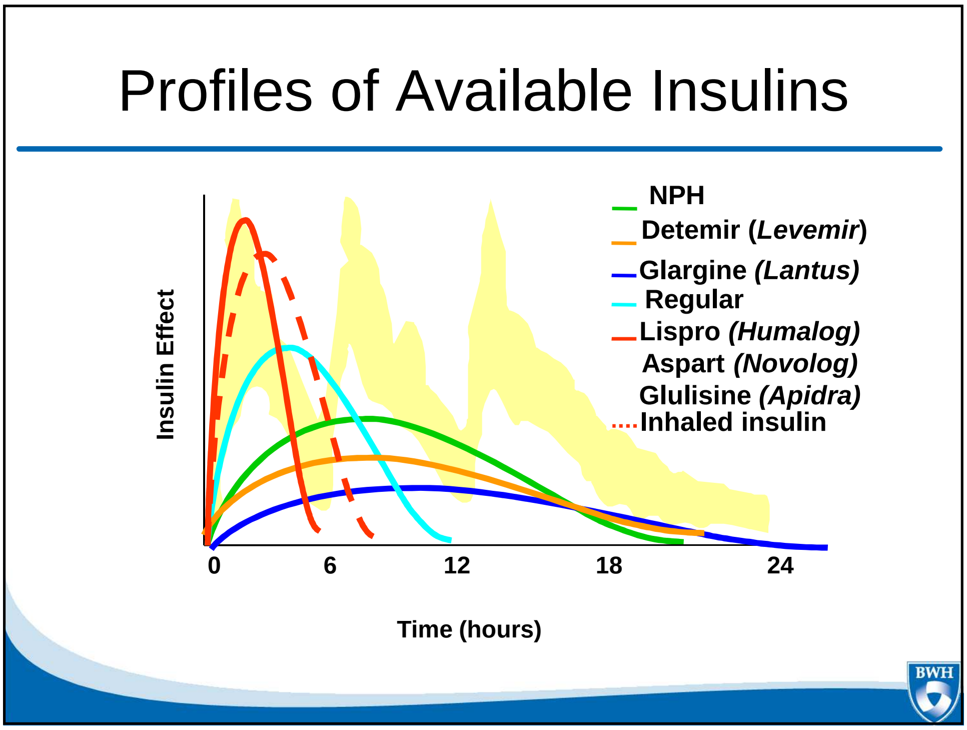


Lodise TP, et al. *Antimicrob Agents Chemother* 2004;48:4718-24



Meropenem 500 mg Administered as a 0.5h or 3-hour Infusion

Dandekar et al. *Pharmacother* 2003;23:988



Profiles of Available Insulins

Safe Use of IV Insulin Therapy

- Insulin infusion concentrations and protocols should be standardized within a hospital
- All MDs/RNs should be trained with competence and assessed regularly
- Accurate bedside blood glucose monitoring done hourly (and if stable, every 2 hours)
- Potassium should be monitored and given if necessary

Clement S, et al. *Diabetes Care*. 2004;27:553–591.

Conclusions

- Critical illness may result in various clinically significant changes in PK
- Monitoring PD goals for clinical effectiveness and adverse effects is of paramount importance
- Frequent evaluation and adjustment to therapy are crucial as course of critical illness evolves
- Alteration in PK/PD can vary widely depending on the nature of critical illness, concurrent disease states, and treatment modalities utilized

Question #1

Which of the following is true regarding metabolism and elimination of commonly used drugs?

A. Phase II reactions which occur in the kidney are responsible for most clinically significant drug-drug interactions

B. A drug's "half-life" is the amount of time necessary for it to achieve steady state in the body

C. The ionized fraction of drugs is reabsorbed by the renal tubules back into the systemic circulation for metabolism by the liver

D. Hepatic enzyme inhibitors increase the half-life of drugs subject to hepatic clearance

E. Cytochrome P450 (CYP)-related metabolic capacity is consistent across different individuals

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E. Cytochrome P450 (CYP)-related metabolic capacity is consistent across different individuals

Question #2

- Which of the following is true regarding the effect of physiologic derangements on medication effects?

A. Cardiovascular derangements alter systemic circulation of transdermally and subcutaneously administered medications, but not their absorption
B. Fluid retention in heart failure decreases the volume of distribution of hydrophilic drugs due to third spacing
C. Insensible losses from burns decrease the volume of distribution of hydrophilic drugs
D. Temporary abdominal closure decreases the volume of distribution of hydrophilic drugs
E. Respiratory failure can alter hepatic clearance of medications

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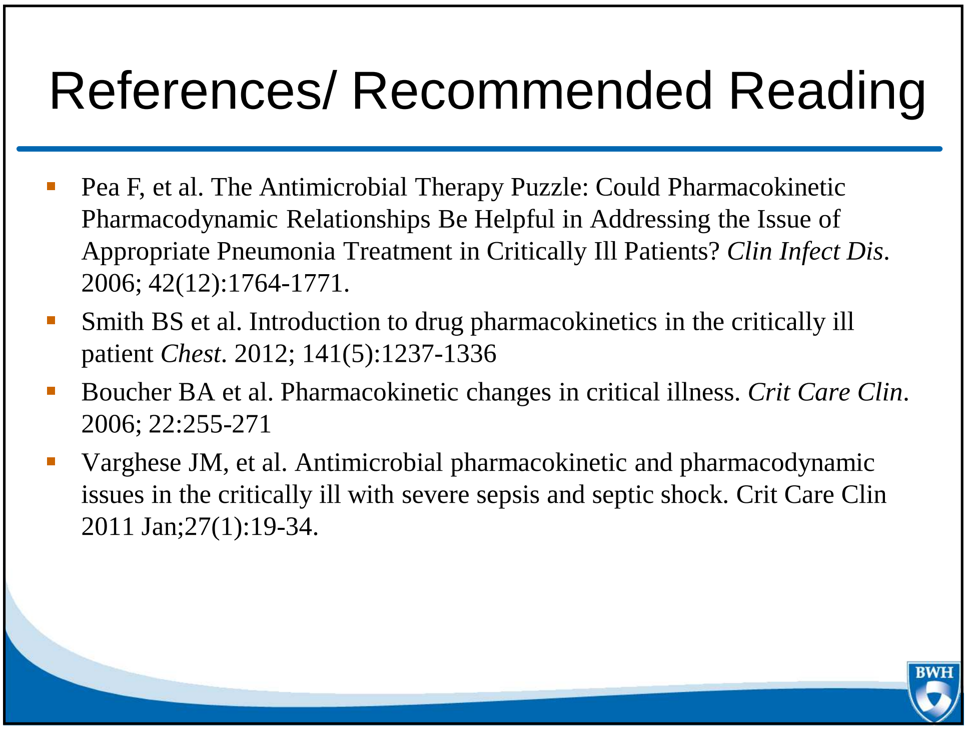

References/ Recommended Reading

- Pea F, et al. The Antimicrobial Therapy Puzzle: Could Pharmacokinetic Pharmacodynamic Relationships Be Helpful in Addressing the Issue of Appropriate Pneumonia Treatment in Critically Ill Patients? *Clin Infect Dis*. 2006; 42(12):1764-1771.
- Smith BS et al. Introduction to drug pharmacokinetics in the critically ill patient *Chest*. 2012; 141(5):1237-1336
- Boucher BA et al. Pharmacokinetic changes in critical illness. *Crit Care Clin*. 2006; 22:255-271
- Varghese JM, et al. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit Care Clin 2011 Jan;27(1):19-34.

Toxic Ingestions

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WOMEN'S HOSPITAL

MASSACHUSETTS
GENERAL HOSPITAL

Disclosures

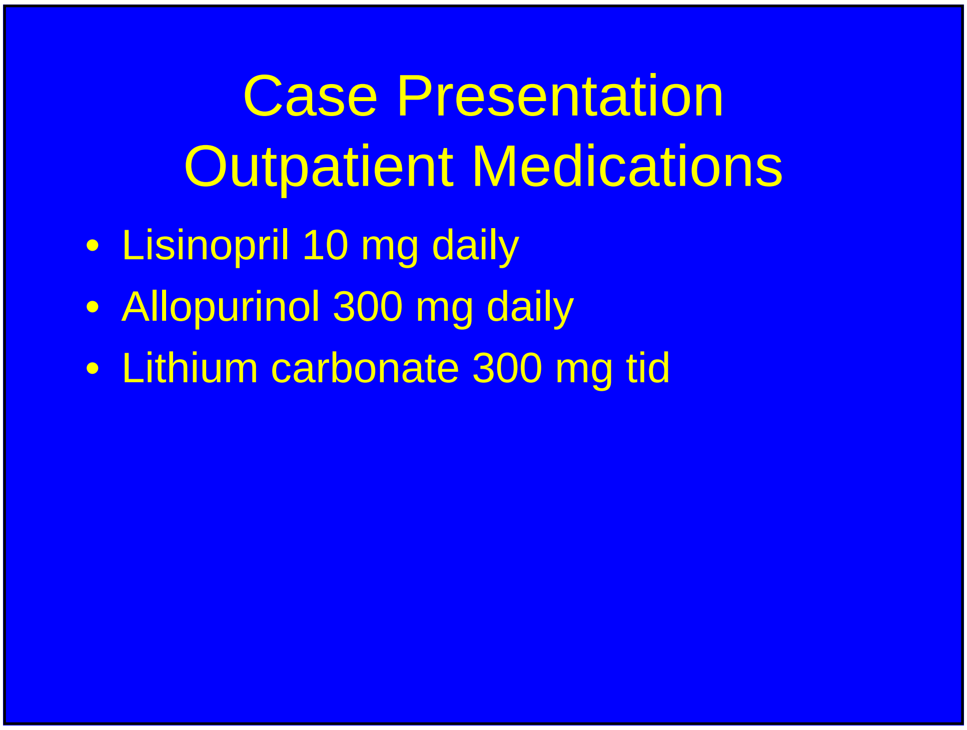
- None

Case Presentation

The patient is a 64-year-old man with a history of bipolar disorder and hypertension. He has normal renal function at baseline. He developed a gastrointestinal illness characterized by nausea, vomiting, and diarrhea. He subsequently became progressively confused with slurred speech and myoclonic jerks.

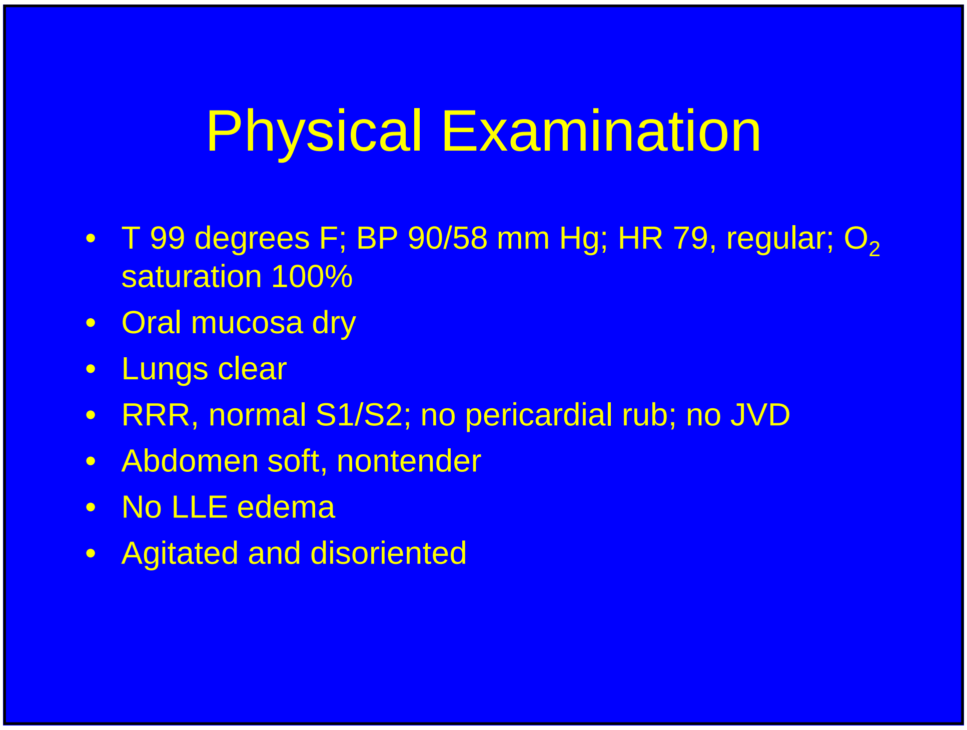
Case Presentation
Past Medical History

- Hypertension
- Bipolar disorder
- Gout



Case Presentation
Outpatient Medications

- Lisinopril 10 mg daily
- Allopurinol 300 mg daily
- Lithium carbonate 300 mg tid



Physical Examination

- T 99 degrees F; BP 90/58 mm Hg; HR 79, regular; O_2 saturation 100%
- Oral mucosa dry
- Lungs clear
- RRR, normal S1/S2; no pericardial rub; no JVD
- Abdomen soft, nontender
- No LLE edema
- Agitated and disoriented

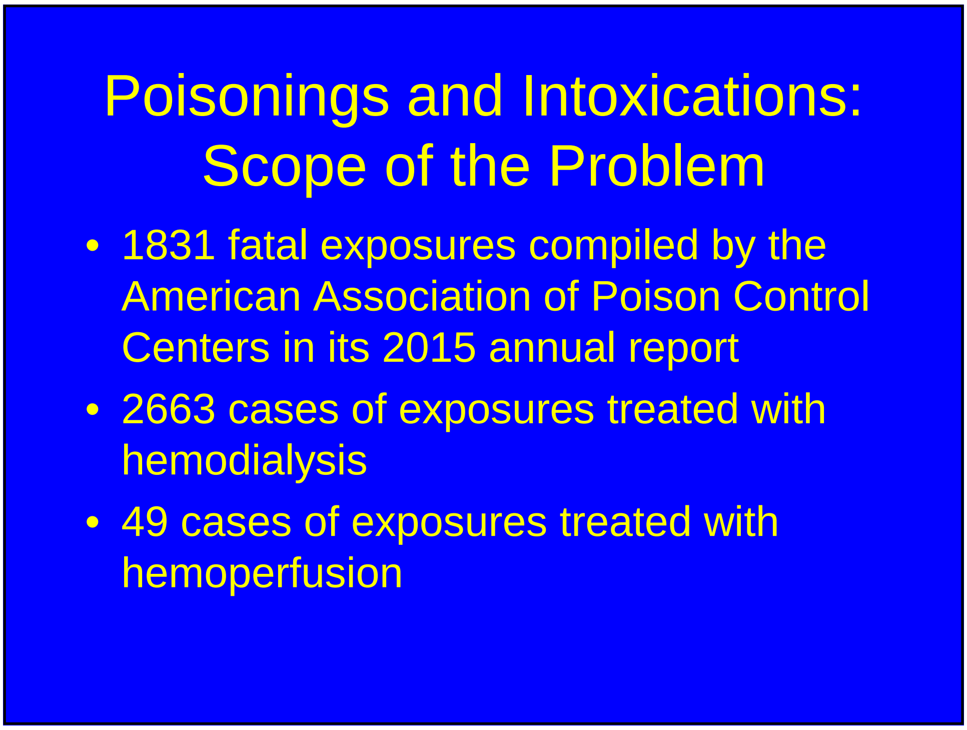
Laboratory Data

- Sodium 146 mEq/L
- Potassium 4.2 mEq/L
- Chloride 110 mEq/L
- CO_2 27 mEq/L
- BUN 48 mg/dL
- Creatinine 3.18 mg/dL
- Calcium 8.7 mg/dL
- Phosphorous 6.1 mg/dL

- WBC 8.9 K/uL
- Hemoglobin 14 g/dL
- Hematocrit 42%
- Platelets 218 K/uL

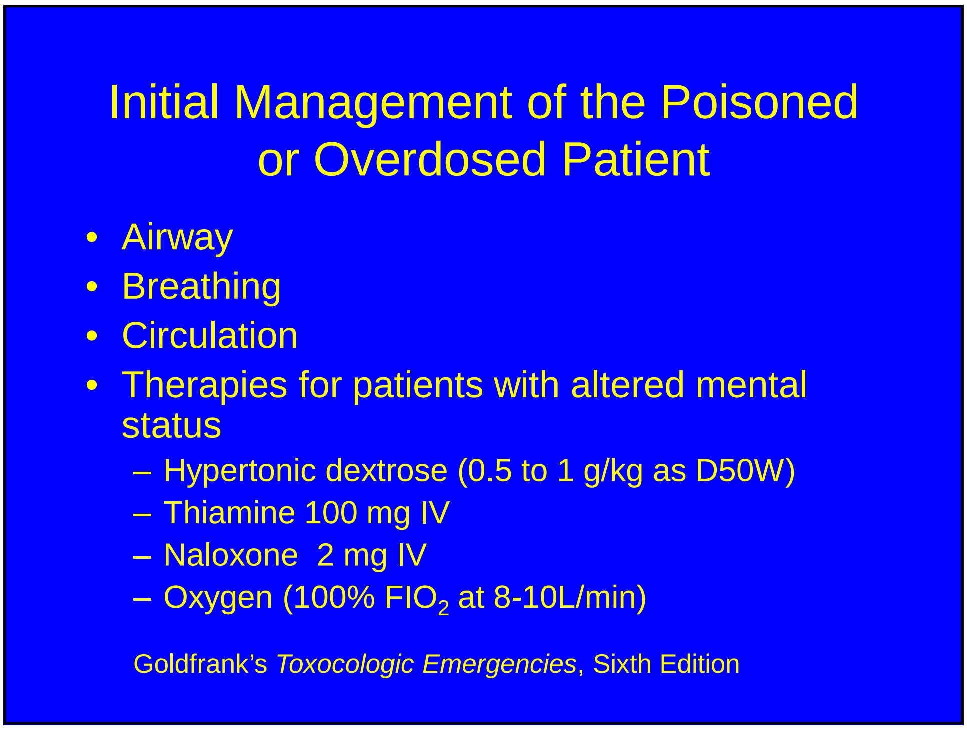
Questions from primary team

- Are his signs and symptoms consistent with lithium toxicity?
- Is there a role for dialysis (or other extracorporeal treatments) in his management?



Poisonings and Intoxications: Scope of the Problem

- 1831 fatal exposures compiled by the American Association of Poison Control Centers in its 2015 annual report
- 2663 cases of exposures treated with hemodialysis
- 49 cases of exposures treated with hemoperfusion



Initial Management of the Poisoned or Overdosed Patient

- Airway
- Breathing
- Circulation
- Therapies for patients with altered mental status
  - Hypertonic dextrose (0.5 to 1 g/kg as D50W)
  - Thiamine 100 mg IV
  - Naloxone 2 mg IV
  - Oxygen (100% FIO_2 at 8-10L/min)

Goldfrank's *Toxocologic Emergencies*, Sixth Edition

Removing the drug or enhancing its elimination

- Removal of the drug from the GI tract
  - Gastric emptying
  - Gastric lavage
- Enhancing elimination through the GI tract
  - Activated charcoal
  - Cathartics
- Enhancing renal elimination of the drug
  - Manipulating urinary pH
  - Forced diuresis

Removing the drug or enhancing its elimination

- Removal of the drug by extracorporeal methods
  - Hemodialysis
  - Hemoperfusion

Manipulation of Urinary pH

- Many toxic compounds are weak acids or bases.
- The ionization of such compounds is dependent upon pKa of the compound and pH of the solution.
- As these substances pass through the kidney, they may be filtered, secreted, and reabsorbed.
- If the urinary pH is manipulated to favor the ionized form, the drug is trapped in luminal fluid and not reabsorbed.

Manipulation of Urinary pH

- For this strategy to be effective, the renal excretion of the compound must be sufficient to make increased clearance a major route of elimination.
- Alkalinization can be achieved by administration of a bicarbonate containing solution
- Goal is to increase urinary pH to 7-8
- Carbonic anhydrase inhibitors should be avoided because of systemic metabolic acidosis

Drugs for which urinary alkalinization may be effective

- Salicylates
- Phenobarbital
- Chlorpropramide

Potential complications of alkalinization

- Volume overload
- Hypernatremia
- Hypocalcemia (ionized)
- Hypokalemia (from bicarbonaturia)

Forced Diuresis

- Increasing urinary flow rate by volume expansion with normal saline may be effective
- Most beneficial for substances in which GFR is an important determinant of excretion, and especially where the extracellular volume is contracted (lithium, for example)

Hemodialysis for intoxications and poisonings

- Hemodialysis is most beneficial for drugs that have specific characteristics:
  - Low volume of distribution (<1 L/kg)
  - Water soluble
  - Low protein binding
  - Rapid equilibration between tissue and blood compartments

Dialysis procedure for poisoning and intoxication

- Choice of dialyzer: High urea clearance; high flux, depending upon molecular weight of substance to be removed
- Bicarbonate concentration may need to be lowered if there is concurrent metabolic alkalosis.
- Phosphorous may need to be supplemented.

Drugs/Toxins efficiently removed by hemodialysis

Drug	Molecular Weight (daltons)	Volume of distribution	Water soluble
Ethylene glycol	62	0.6	Yes
Isopropanol	60	0.6	Yes
Lithium	7	0.6-1.0	Yes
Methanol	32	0.7	Yes
Salicylate	138	0.2	Yes
Theophylline	180	0.5	Yes

Hemoperfusion

- A technique in which blood is passed through a cartridge packed with charcoal or carbon
- Charcoal in the cartridge competes with plasma protein for the drug, adsorbs it, and eliminates it from the circulation
- More efficient at removing lipid soluble drugs than is hemodialysis.

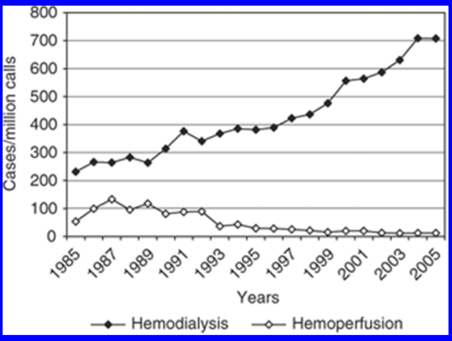
Hemoperfusion

- Requires more heparin than hemodialysis
- Qb typically 250 to 400 mL/min
- Some charcoal cartridges require priming with D5W to load the cartridge with glucose

Drugs/Toxins efficiently removed by hemoperfusion

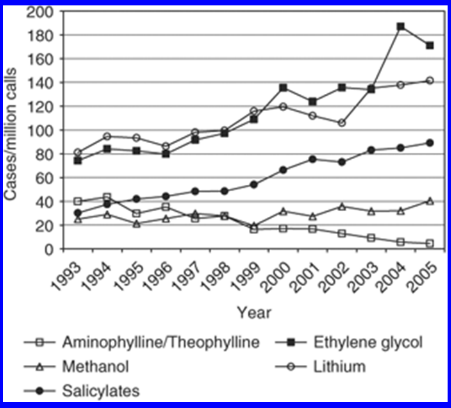
Drug	Molecular Weight (daltons)	Volume of distribution	Water soluble
Theophylline	180	0.5	Yes
Carbamazepine	236	1.4	No
Disopyramide	340	0.6	No
Phenobarbital	232	0.5	No
Phenytoin	252	0.6	No

Number of cases receiving hemodialysis and hemoperfusion



Holubek *et al*, Kidney Int 74: 1327-34, 2008

Trends for commonly accepted indications for HD and/or HP



Holubek *et al*, Kidney Int 74: 1327-34, 2008

Availability of Hemoperfusion

- Charcoal hemoperfusion cartridges in only one-third of New York City hospitals receiving emergency patients
- Only three in-hospital hemodialysis units in New York City had performed hemoperfusion in the last five years, on three cases.

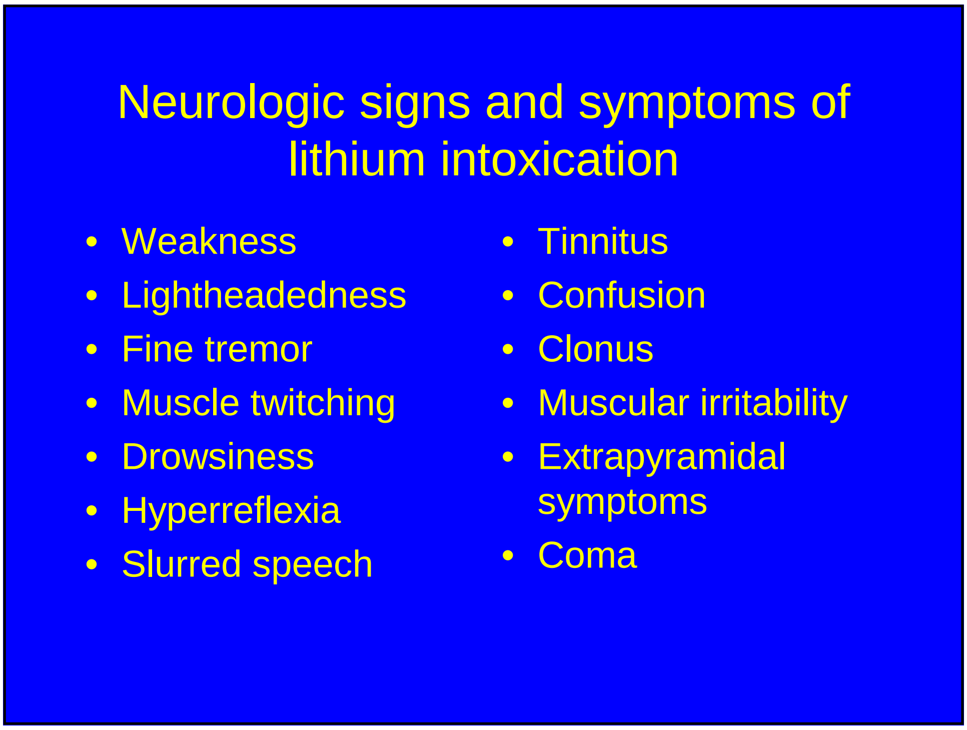
Shalkham *et a*l, Am J Kidney Dis 48: 239-241, 2006

Lithium

- Lithium is a monovalent cation that is used to treat bipolar disorder
- It has a narrow therapeutic window.
- Rapidly absorbed from the GI tract
- Peak levels occur at 2-4 hours
- Large volume of distribution (0.6-0.9 L/kg)
- Excreted by the kidney

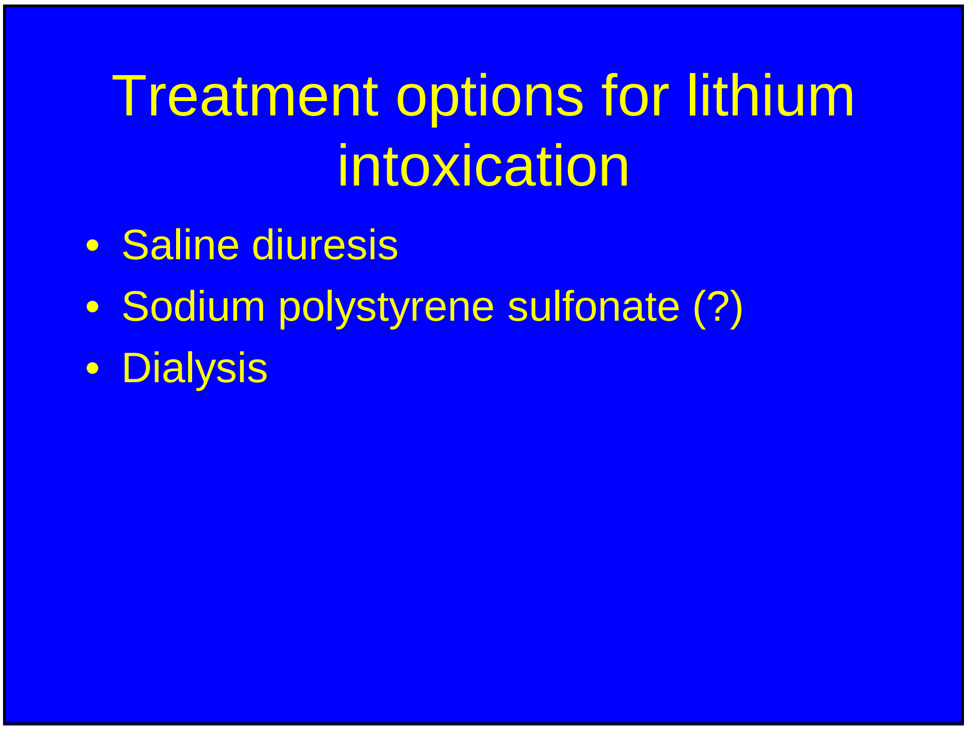
Signs of lithium intoxication

- Prolonged QT interval
- Nausea, vomiting
- Leucocytosis
- Urine concentrating defects



Neurologic signs and symptoms of lithium intoxication

- Weakness
- Lightheadedness
- Fine tremor
- Muscle twitching
- Drowsiness
- Hyperreflexia
- Slurred speech
- Tinnitus
- Confusion
- Clonus
- Muscular irritability
- Extrapyramidal symptoms
- Coma



Treatment options for lithium intoxication

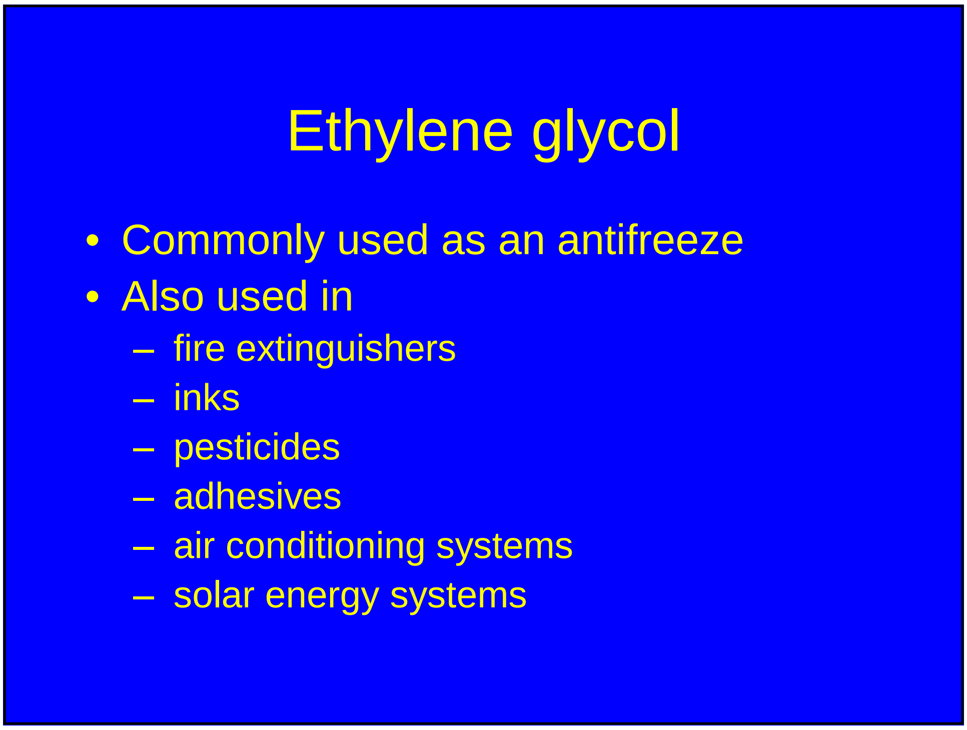
- Saline diuresis
- Sodium polystyrene sulfonate (?)
- Dialysis

Indications for hemodialysis

- Altered mental status
- Renal dysfunction
- Inability to tolerate a sodium load
- Level ≥ 4.0 mEq/L in acute toxicity
- Level ≥ 2.5 mEq/L in chronic toxicity
- Watch for rebound; a second treatment may be required

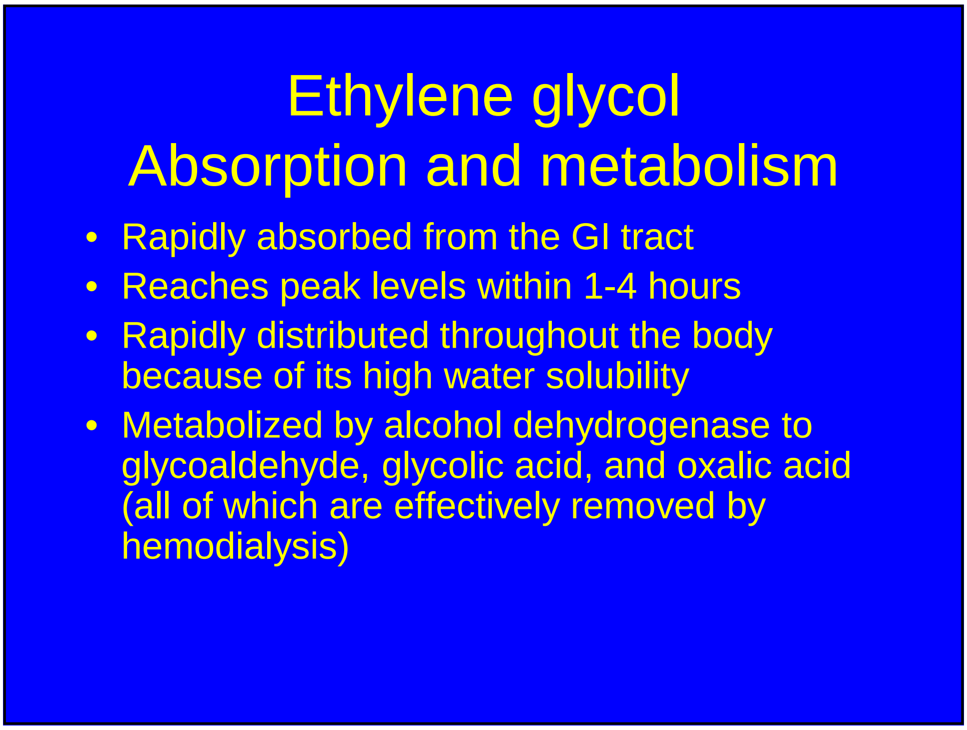
Toxic Alcohols

- The three toxic alcohols most commonly associated with toxicologic emergencies:
  - methanol
  - ethylene glycol
  - isopropanol



Ethylene glycol

- Commonly used as an antifreeze
- Also used in
  - fire extinguishers
  - inks
  - pesticides
  - adhesives
  - air conditioning systems
  - solar energy systems



Ethylene glycol
Absorption and metabolism

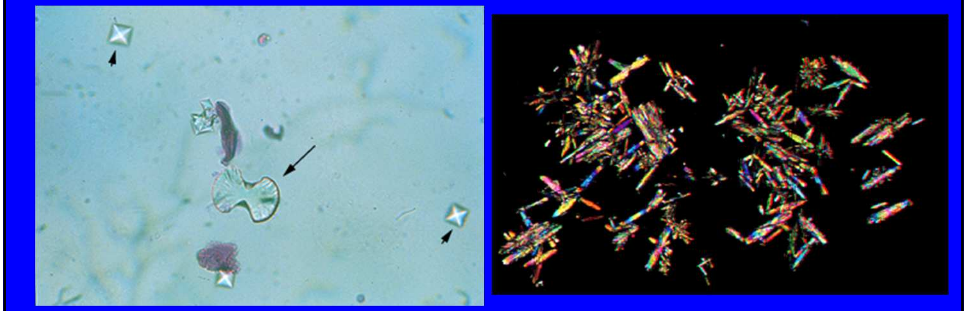
- Rapidly absorbed from the GI tract
- Reaches peak levels within 1-4 hours
- Rapidly distributed throughout the body because of its high water solubility
- Metabolized by alcohol dehydrogenase to glycoaldehyde, glycolic acid, and oxalic acid (all of which are effectively removed by hemodialysis)

Clinical findings in ethylene glycol intoxication

- Nausea/vomiting
- Lethargy
- Coma
- Nystagmus
- Ataxia
- Areflexia
- Myoclonic movements
- Seizures

- Anion-gap metabolic acidosis
- Osmolal gap
- Oxalate cystals in urine
- Hippurate crystals in urine
- Hypocalcemia
- ATN

Examination of the urine



- Crystalluria can persist for up to 40 hrs with normal renal function, and 4 days with renal failure
- Dihydrate crystals (4-5hrs)
- Mix of dihydrate and monohydrate crystals (5-7 hrs)
- Only monohydrate crystals (> 7 hrs)

- Urine fluorescence under UV light (wavelength 360 nm) with a Wood’s lamp is pH dependent
- Fluorescence will be minimal or absent with urine pH ≤ 4.5
- Not all brands of anti-freeze have sodium fluorescein added

Methanol

- A commonly used alcohol found in
  - Windshield washing and de-icing solutions
  - Carburetor cleaners
  - Duplicating fluids
  - Solid canned fuels
  - Shellac
  - Paint removers and thinners
  - Embalming fluids

Methanol
Absorption and metabolism

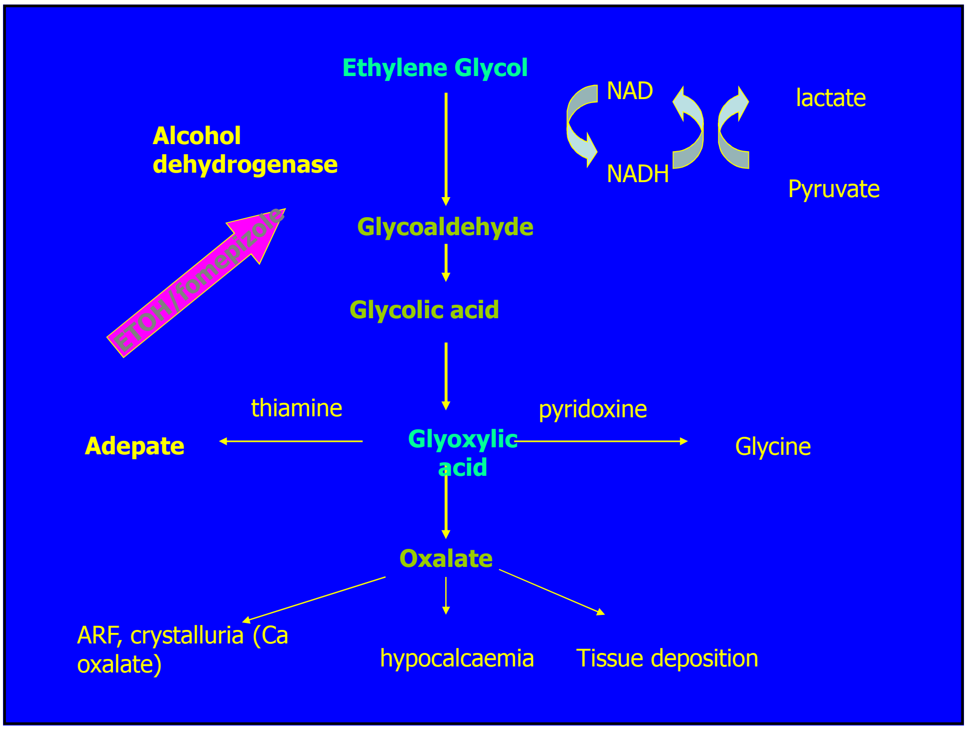
- Peak levels occurs within 30-60 minutes
- Often a latent period of about 24 hours before development of either toxic symptoms or metabolic acidosis
- Volume of distribution of 0.6-0.7L/kg
- 75-85% is metabolized in the liver by alcohol dehydrogenase; 10-20% excreted unchanged by the lungs

Methanol Metabolites

- Alcohol dehydrogenase metabolizes methanol to formaldehyde.
- Formaldehyde is then oxidized to formic acid, which produces the metabolic acidosis and the retinal toxicity.

Clinical findings in methanol intoxication

- Tachycardia
- Hypotension
- Seizures
- Coma
- Headache
- Somnolence
- Abdominal pain
- Nausea/vomiting
- Blurred vision
- Hyperemic optic discs
- Papilledema
- Blindness
- Hemorrhagic and non-hemorrhagic necrosis of the putamen



Ethylene Glycol

Alcohol dehydrogenase

EtOH/fomepizole

NAD

NADH

lactate

Pyruvate

Glycoaldehyde

Glycolic acid

thiamine

pyridoxine

Adepate

Glyoxylic acid

Glycine

Oxalate

ARF, crystalluria (Ca oxalate)

hypocalcaemia

Tissue deposition

Treatment of methanol and ethylene glycol intoxications

- Blocking alcohol dehydrogenase
  - Ethanol
  - Fomepizole
- Hemodialysis
  - Correction of metabolic abnormalities
  - Removal of toxic metabolites

Treatment of methanol and ethylene glycol intoxications

- Thiamine and Pyridoxine (ethylene glycol)
  - Thiamine 100 mg IV q 6 hours (shunts metabolism of glyoxylic acid to alpha-hydroxy-beta-ketoadipic acid)
  - Pyridoxine 50 mg IV q 6 hours (shunts metabolism from glyoxylic acid to glycine)
- Folate (methanol)
  - 50-75 mg IV q 4 hours for 24 hours to enhance elimination of formic acid

Indications for hemodialysis in ethylene glycol poisonings

- Severe metabolic acidosis (pH 7.25-7.3) unresponsive to therapy
- Renal failure
- Ethylene glycol levels > 50 mg/dL unless fomepizole is being administered and patient is asymptomatic with a normal pH

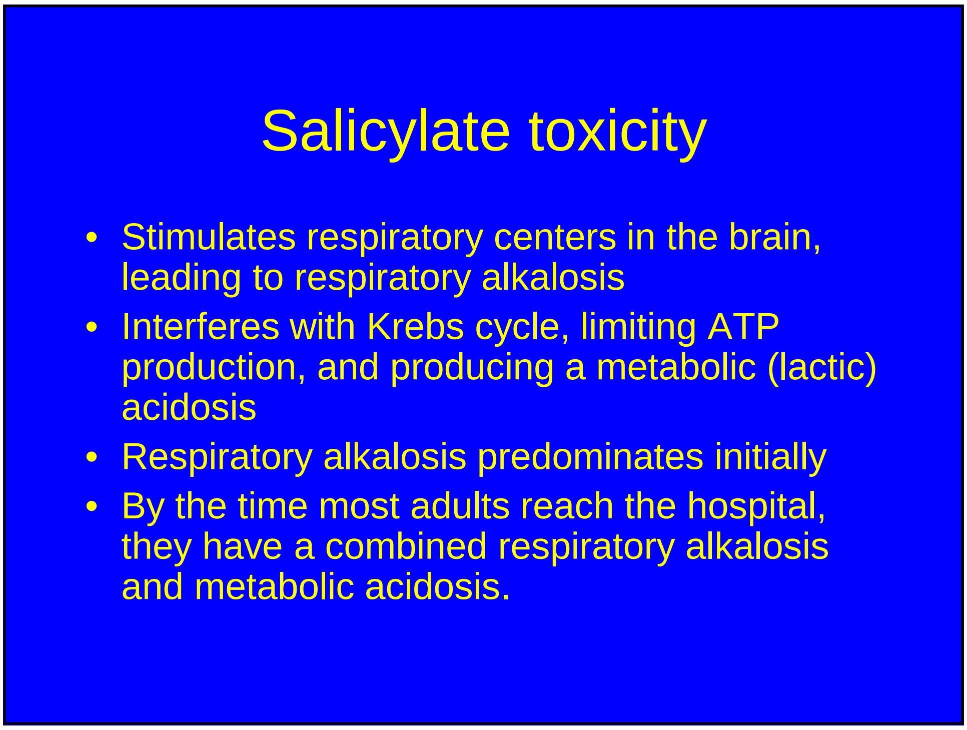
From Winchester and Kitiyakara in *Handbook of Dialysis*

Indications for dialysis in methanol poisoning

- Methanol level > 50 mg/dL
- Visual, fundoscopic, or mental status changes
- Severe acidosis
- Serum formic acid levels elevated
- Consumption of the equivalent of more than 30 mL of pure methanol

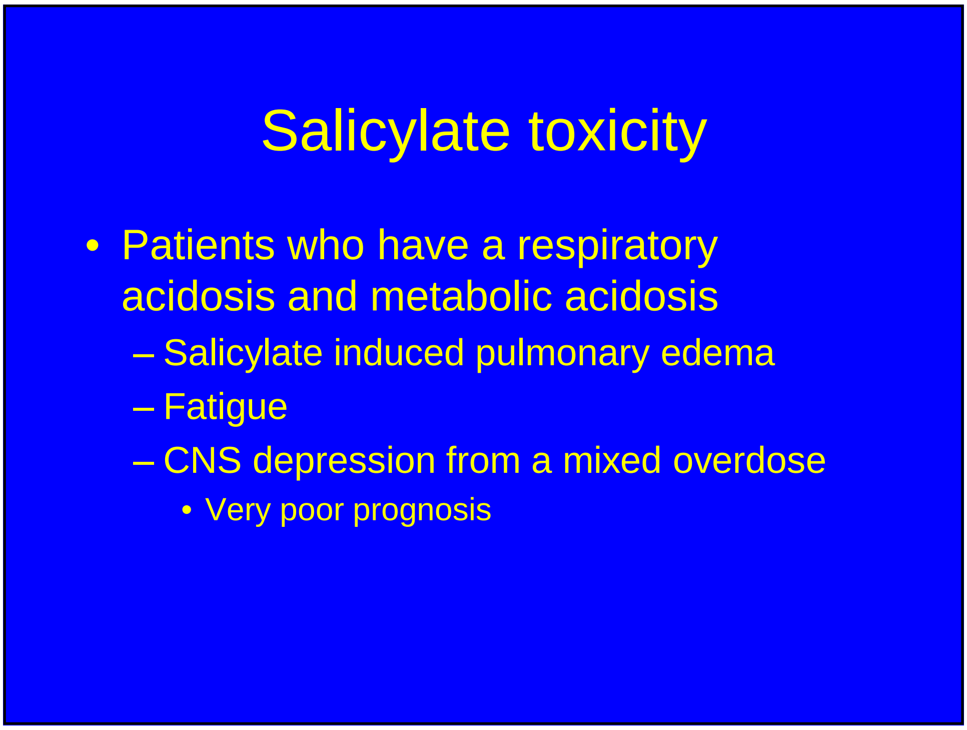
Salicylates

- The active ingredient in the common pain preparation aspirin
- May be found in combination with other drugs, e.g., caffeine in some preparations



Salicylate toxicity

- Stimulates respiratory centers in the brain, leading to respiratory alkalosis
- Interferes with Krebs cycle, limiting ATP production, and producing a metabolic (lactic) acidosis
- Respiratory alkalosis predominates initially
- By the time most adults reach the hospital, they have a combined respiratory alkalosis and metabolic acidosis.



Salicylate toxicity

- Patients who have a respiratory acidosis and metabolic acidosis
  - Salicylate induced pulmonary edema
  - Fatigue
  - CNS depression from a mixed overdose
    - Very poor prognosis

Clinical features of salicylate poisoning

- Anion-gap metabolic acidosis
- Respiratory alkalosis
- Tinnitus
- Deafness
- Vertigo
- Hallucinations
- Stupor
- Seizures
- Coma
- Nausea/vomiting
- Gastritis
- Pylorospasm
- Abnormal LFTs
- Hypoglycemia
- Hyperthermia

Bedside testing for salicylates

- Add several drops of $FeCl_3$ to 1 mL of urine
- Purple color indicates the presence of salicylic acid, acetoacetic acid, or phenylpyruvic acid
- Highly sensitive for small quantities of salicylic acid

Alkalinization of urine and blood

- Salicylic acid is a weak acid (pKa 3.5)
- It is thus “trapped” in an alkaline environment
- Alkalinization of the urine enhances its excretion
- Alkalinzation of the blood keeps it out of the CNS
- Alkalinization should be considered whenever the level is > 35 mg/dL
- Goal urine pH 7.5-8.0

Indications for hemodialysis in salicylate poisoning

- Renal failure
- Congestive heart failure
- Noncardiogenic pulmonary edema
- Persistent CNS disturbances
- Progressive deterioration in vital signs
- Severe acid-base or electrolyte disturbances
- Hepatic compromise with coagulopathy
- Salicylate level (acute) > 100 mg/dL

Amphetamine and related drugs of abuse

- Methamphetamine is a sympathomimetic amine that belongs to the class of phenethylamines.
- Amphetamine was first synthesized in Germany in 1887.
- Plant-derived stimulant ephedra (ma huang) containing the alkaloids ephedrine and pseudoephidrine has been used in traditional Chinese medicine for more than 5000 years to treat asthma and the common cold.

History of Amphetamines

- A nasal decongestant containing amphetamine was marketed in 1932.
- Widespread abuse led the FDA to ban amphetamine inhalers in 1959.
- The passage of the Controlled Substances Act in 1970 reduced the rates of amphetamine abuse.
- The 1990s saw the explosion of “designer” amphetamines.

Methamphetamine

- After cannabis, the most widely used drug of abuse in the United States.
- About 5% of the US population are estimated to have used meth, with about 300,000 new users each year.
- Used clinically for the treatment of ADHD, narcolepsy and short-term treatment of obesity.
- Can easily be synthesized in home labs from over-the-counter cold preparations.

Methamphetamine’s effects

- Meth is taken up by cytoplasmic vesicles of presynaptic adrenergic neurons, thus displacing epinephrine, norepinephrine, dopamine, and serotonin.

  α and β adrenergic receptors:
  - Hypertension, tachycardia, vasospasm, hyperthermia
- Dopamine receptor stimulation:
  - Drug craving and psychiatric symptoms
- Serotonergic stimulation:
  - Mood alterations; abnormal response to hunger and thirst

Clinical Features of Meth Intoxication

- Tachycardia
- Hyperthermia
- Agitation
- Psychosis
- Diaphoresis
- Minimally reactive mydriasis

Clinical Features of Meth Intoxication for Which Nephrology May be Consulted

- Hypertension
  - Avoid β blockers, which would lead to unopposed α stimulation
- Acute Renal Failure
  - Rhabdomyolysis
  - Renal hypoperfusion/ischemia
- Hyponatremia
  - Excess water intake
  - SIADH

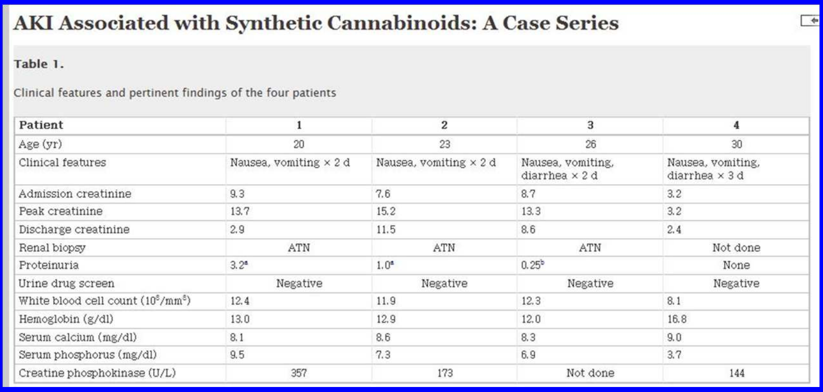
Synthetic cannabinoids

- Commonly known as spice or K2
- Used recreationally but marketed as
  - Incense products
  - Bath additives
  - Air fresheners

Synthetic cannabinoids

- Distributed in the form of dried leaves, resin, or powder
- Typically a mixture of synthetic cannabinoids and herbal additive
- Mixture is typically smoked in a pipe or “hookah,” although inhalation and ingestion have also been described

AKI associated with spice



AKI Associated with Synthetic Cannabinoids: A Case Series

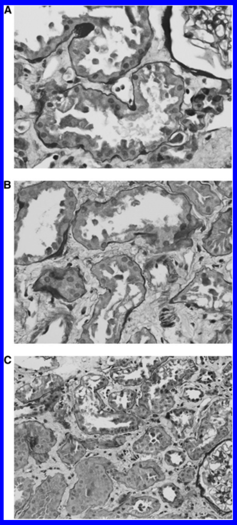
Table 1.

Clinical features and pertinent findings of the four patients

Patient	**1**	**2**	**3**	**4**
Age (yr)	20	23	26	30
Clinical features	Nausea, vomiting × 2 d	Nausea, vomiting × 2 d	Nausea, vomiting, diarrhea × 2 d	Nausea, vomiting, diarrhea × 3 d
Admission creatinine	9.3	7.6	8.7	3.2
Peak creatinine	13.7	15.2	13.3	3.2
Discharge creatinine	2.9	11.5	8.6	2.4
Renal biopsy	ATN	ATN	ATN	Not done
Proteinuria	3.2[a]	1.0[a]	0.25[b]	None
Urine drug screen	Negative	Negative	Negative	Negative
White blood cell count ($10^3/mm^3$)	12.4	11.9	12.3	8.1
Hemoglobin (g/dl)	13.0	12.9	12.0	16.8
Serum calcium (mg/dl)	8.1	8.6	8.3	9.0
Serum phosphorus (mg/dl)	9.5	7.3	6.9	3.7
Creatine phosphokinase (U/L)	357	173	Not done	144

Bhanushali GK *et al*. Clin J Am Soc Nephrol 2013;8:523-526

Pathologic features of kidney injury from spice



Bhanushali GK *et al*. Clin J Am Soc Nephrol 2013;8:523-526

Summary

- Removal of drug via the GI tract
  - Gastric emptying
  - Charcoal adsorption
- Enhanced renal elimination
  - Saline diuresis
  - Alkalinization
- Extracorporeal therapies
  - Hemodialysis
  - Hemoperfusion
- Specific antidotes
  - Fomepizole
  - Ethanol

Serum concentrations of commons poisons in excess of which hemodialysis or hemoperfusion should be considered

Drug	Concentration	Method of Choice
Theophylline	40 mg/L	HP > HD
Phenobarbital	100 mg/L	HP > HD
Salicylates	1000 mg/L	HD
Ethylene Glycol	500 mg/L	HD
Methanol	500 mg/L	HD
Lithium acute	4.0 mEq/L	HD
Lithium chronic	2.5 mEq/L	HD

Conventional Wisdom Regarding Dialysis in Poisonings

- Has been based upon obsolete technology
- Very few clinical trials to examine the role of modern extracorporeal therapies in poisonings and intoxications

Modern advances in extracorporeal therapies

- High-flux and high efficiency dialyzers are now standard in most hospitals
- These dialyzers have superior molecular cutoff and greater ultrafiltration coefficents than older cuprophane dialyzers.
- Newer catheters achieve greater blood flow, also enhancing poison removal.

Protein binding

- In poisoning, protein binding sites become saturated.
- The proportion of free (dialyzable) drug therefore increases.
- Even if the proportion of bound drug remains significant, it can dissociate rapidly from its binding sites, assuming it has a small binding constant.

Case Presentation

- This patient has acute kidney injury in the setting of nausea, vomiting, diarrhea coupled with ACE-I use.
- BP remains low, suggesting ongoing volume depletion.

Follow-up

- Lithium level is 4.1 mEq/L.
- IV normal saline is administered with restoration of circulatory volume and rapid improvement in renal function.
- Dialysis is not required since lithium level falls quickly as GFR increases.

Question 1

- Hemodialysis is most effective at removing drugs/toxins with which of the following characteristics?
  - A) Highly protein bound
  - B) Low volume of distribution
  - C) Lipid soluble
  - D) Slowly equilibrates between blood and tissue compartments

Question 1

- Hemodialysis is most effective at removing drugs/toxins with which of the following characteristics?
  - A) Highly protein bound
  - B) **Low volume of distribution**
  - C) Lipid soluble
  - D) Slowly equilibrates between blood and tissue compartments

Question 1 Explanation

- Hemodialysis is most effective at removing drugs that are water soluble and not protein bound. It is also most effective at removing drugs that rapidly equilibrate between the blood and tissue compartments. Therefore, the best answer is choice B.

Question 2

- Which of the following may be used to block the metabolism of ethylene glycol to toxic metabolites?
  - A) Ethanol
  - B) Fomepizole
  - C) Thiamine
  - D) Pyridoxine
  - E) All of the above

Question 2

- Which of the following may be used to block the metabolism of ethylene glycol to toxic metabolites?
  - A) Ethanol
  - B) Fomepizole
  - C) Thiamine
  - D) Pyridoxine
  - E) **All of the above**

Question 2 Explanation

- Ethanol and fomepizole both block alcohol dehydrogenase, thereby limiting the metabolism of ethylene glycol and the production of toxic metabolites. Thiamine and pyridoxine both shunt the metabolism of glyoxylic acid away from the production of oxalate. The best answer is therefore E.

Question 3

- Charcoal hemoperfusion would be more efficacious than hemodialysis in removal of which of the following drugs?
  - A) Lithium
  - B) Ethylene glycol
  - C) Theophylline
  - D) Methanol
  - E) Salicylate

Question 3

- Charcoal hemoperfusion would be more efficacious than hemodialysis in removal of which of the following drugs?
  - A) Lithium
  - B) Ethylene glycol
  - C) **Theophylline**
  - D) Methanol
  - E) Salicylate

Question 3 Explanation

- Theophylline is more highly protein bound and lipid soluble than each of the other compunds which are very effectively removed by hemodialysis. Therefore the best answer is c.

References

- Holubek *et al*, Kidney Int 74: 1327-34, 2008
- Shalkham *et a*l, Am J Kidney Dis 48: 239-241, 2006
- Bhanushali GK et al. Clin J Am Soc Nephrol 2013;8:523-526
- Kraut JA and Kurtz I, Clin J Am Soc Nephrol 3: 208-225, 2008

Disclosures

- None

Sedation and Delirium in the ICU

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Associate physician, Brigham and Women's Hospital
Assistant professor of Medicine, Harvard Medical School

BRIGHAM AND WOMEN'S HOSPITAL
| The Lung Center |

Disclosures

- None

Delirium: What is it?
It is a syndrome, not a disease.

- **Disturbance in consciousness**
- **Change in cognition or development of perceptual disturbance not accounted for by pre-existing or evolving dementia**
- **Disturbance develops over hours-days and fluctuates in severity**

- "Syndrome":
  - An aggregate of signs and symptoms associated with any morbid process and constituting together the picture of the disease

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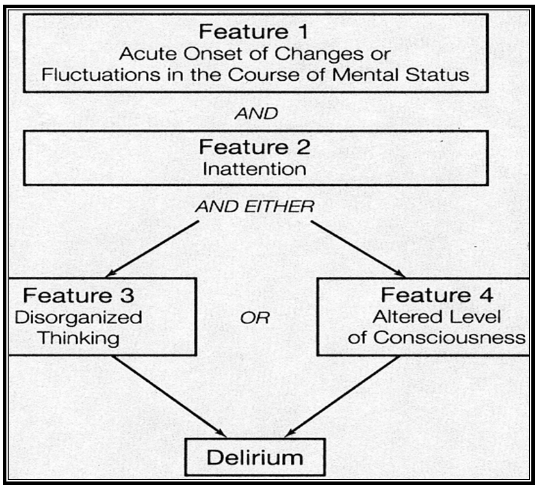
Delirium assessment tool:
CAM-ICU


Feature 1
Acute Onset of Changes or Fluctuations in the Course of Mental Status
AND
Feature 2
Inattention
AND EITHER
Feature 3
Disorganized Thinking
OR
Feature 4
Altered Level of Consciousness
Delirium

Delirium recognition

- **Delirium is often invisible in ICU**
- **Most ICU delirium is hypoactive subtype (35%) or mixed (64%)**
- **PURE hyperactive subtype is rare**
- **Older age is a strong predictor of hypoactive type**
- **Onset ICU Day 2 (+/- 1.7 days)**

- **3+ Types of delirium:**
  - Hyperactive
  - Hypoactive: most common in the elderly
  - Mixed

Ely EW JAMA 2001;286:2703
McNicoll L JAGS 2003;51:591
Ely EM CCM 2001;9:1370

Core Points: ICU Delirium

- **60% to 80% of mechanically ventilated patients develop delirium**

- 20% to 50% of lower severity ICU patients develop delirium

Ely EW JAMA 2001;286,2703-2710
Ely EW CCM 2001;29,1370-79
McNicoll L, JAGS 2003;51:591-98

Delirium epidemiology in critical care (DECCA): an international study

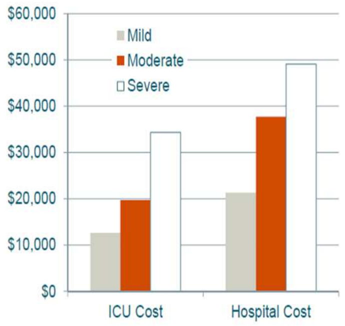
Jorge I Salluh[1*], Márcio Soares[1], José M Teles[2], Daniel Ceraso[3], Nestor Raimondi[3], Victor S Nava[4], Patrícia Blasquez[1], Sebastian Ugarte[5], Carlos Ibanez-Guzman[6], José V Centeno[7], Manuel Laca[8], Gustavo Grecco[9], Edgar Jimenez[10], Susana Árias-Rivera[11], Carmelo Duenas[12], Marcelo G Rocha[13],
The DECCA (Delirium Epidemiology in Critical Care) Study Group

- November 27,2009
- 104 ICU’s, 3 continents
- 75/232 (32%) delirious

Salluh *et al. Critical Care* 2010, **14**:R210

Core Points Regarding ICU Delirium

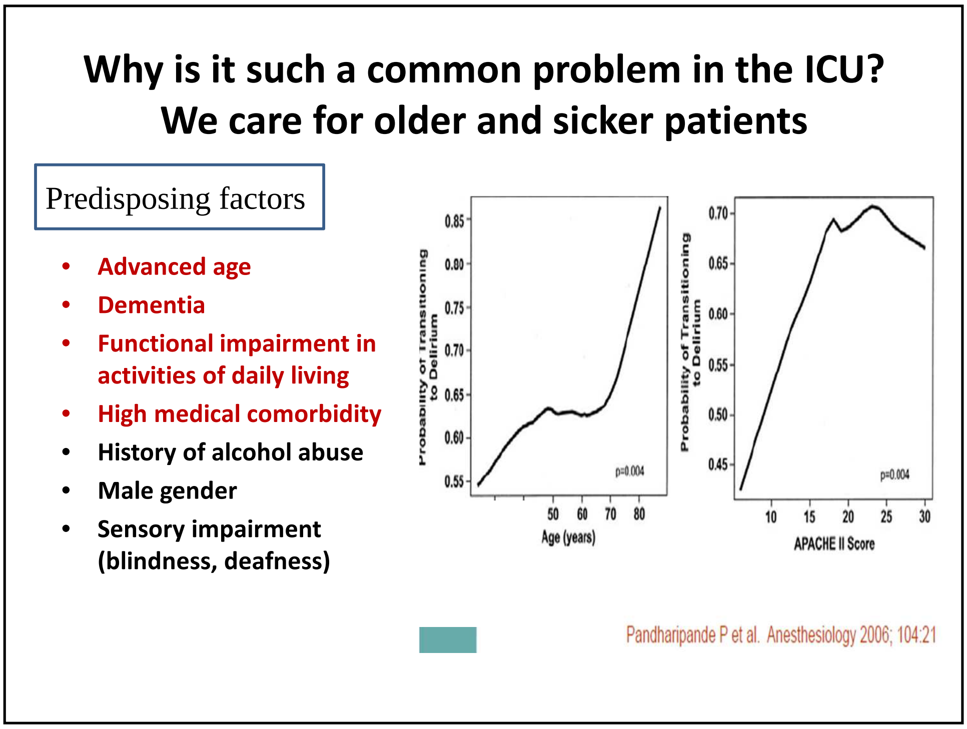
- $15k to $25k higher hospital costs
- Estimated national $4 to $16 billion associated costs



Financial cost of delirium (by severity)

Milbrandt E et al. CCM 2004;32:955

Ely EW et al, JAMA 2004;291-1753-1762

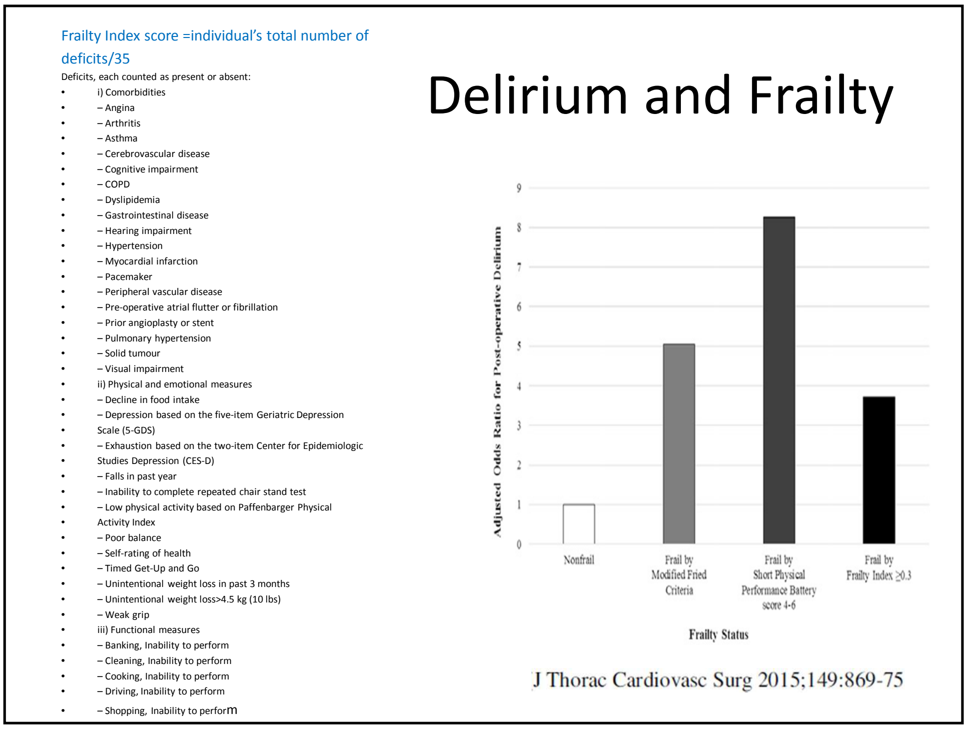


Why is it such a common problem in the ICU?
We care for older and sicker patients

Predisposing factors

- Advanced age
- Dementia
- Functional impairment in activities of daily living
- High medical comorbidity
- History of alcohol abuse
- Male gender
- Sensory impairment (blindness, deafness)

Pandharipande P et al. Anesthesiology 2006; 104:21



Frailty Index score =individual's total number of deficits/35

Deficits, each counted as present or absent:

- i) Comorbidities
- – Angina
- – Arthritis
- – Asthma
- – Cerebrovascular disease
- – Cognitive impairment
- – COPD
- – Dyslipidemia
- – Gastrointestinal disease
- – Hearing impairment
- – Hypertension
- – Myocardial infarction
- – Pacemaker
- – Peripheral vascular disease
- – Pre-operative atrial flutter or fibrillation
- – Prior angioplasty or stent
- – Pulmonary hypertension
- – Solid tumour
- – Visual impairment
- ii) Physical and emotional measures
- – Decline in food intake
- – Depression based on the five-item Geriatric Depression
- Scale (5-GDS)
- – Exhaustion based on the two-item Center for Epidemiologic
- Studies Depression (CES-D)
- – Falls in past year
- – Inability to complete repeated chair stand test
- – Low physical activity based on Paffenbarger Physical
- Activity Index
- – Poor balance
- – Self-rating of health
- – Timed Get-Up and Go
- – Unintentional weight loss in past 3 months
- – Unintentional weight loss>4.5 kg (10 lbs)
- – Weak grip
- iii) Functional measures
- – Banking, Inability to perform
- – Cleaning, Inability to perform
- – Cooking, Inability to perform
- – Driving, Inability to perform
- – Shopping, Inability to perform

Delirium and Frailty

Adjusted Odds Ratio for Post-operative Delirium
9
8
7
6
5
4
3
2
1
0
Nonfrail
Frail by Modified Fried Criteria
Frail by Short Physical Performance Battery score 4-6
Frail by Frailty Index ≥0.3
Frailty Status

J Thorac Cardiovasc Surg 2015;149:869-75

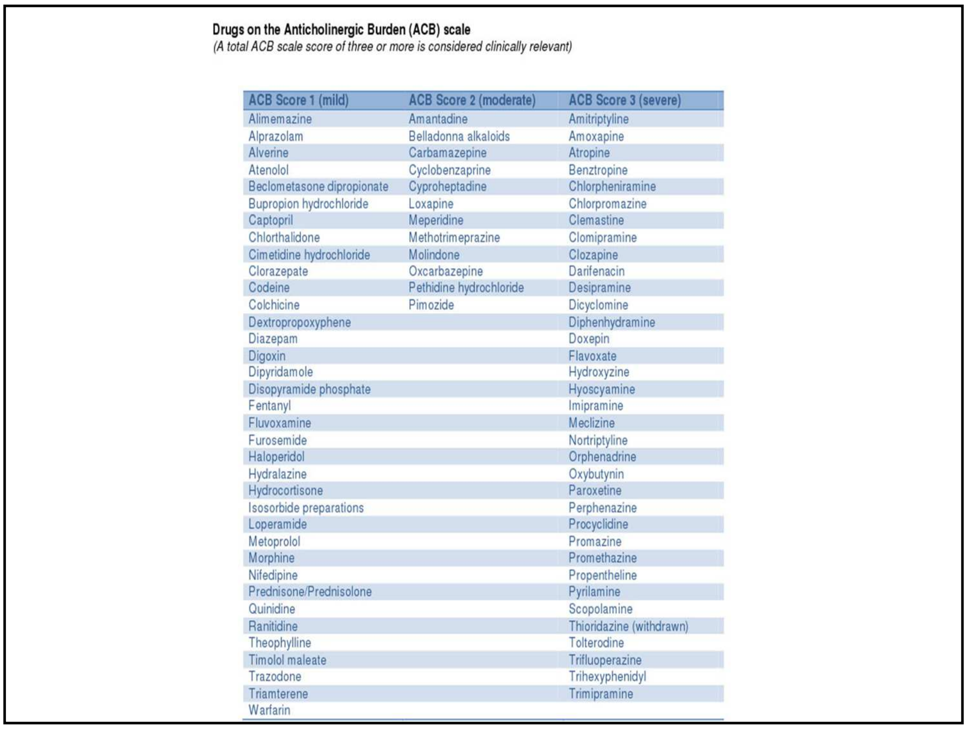
RISK FACTORS:

Think iatrogenic

- Bed rest
- Drug withdrawal
- Fluid or electrolyte disturbances, including dehydration etc
- Infections (especially respiratory, urinary)
- Use of indwelling devices, such as urinary catheters
- Use of restraints
- Medications
- Severe anemia (hematocrit < 30%)
- Uncontrolled pain
- Urinary retention
- Fecal impaction

Common medications associated with ICU delirium

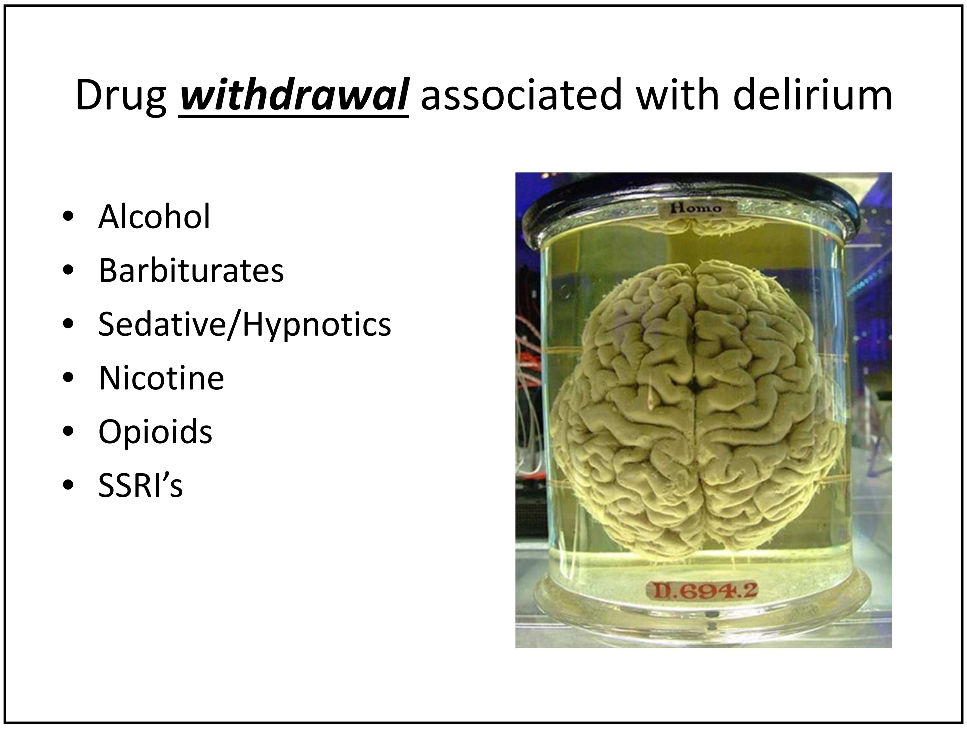
- Analgesics:
  - Meperidine, opiates, NSAIDS
- Sedative-hypnotics
  - BENZODIAZEPINES*
  - Barbiturates
- Anticholinergics:
  - Antidepressants
  - Antipsychotics
  - Antihistamines
  - Antispasmodics
  - Antiemetics
  - Antiparkinsonians
  - Cardiovascular



Drugs on the Anticholinergic Burden (ACB) scale

(A total ACB scale score of three or more is considered clinically relevant)

ACB Score 1 (mild)	ACB Score 2 (moderate)	ACB Score 3 (severe)
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Belladonna alkaloids	Amoxapine
Alverine	Carbamazepine	Atropine
Atenolol	Cyclobenzaprine	Benztropine
Beclometasone dipropionate	Cyproheptadine	Chlorpheniramine
Bupropion hydrochloride	Loxapine	Chlorpromazine
Captopril	Meperidine	Clemastine
Chlorthalidone	Methotrimeprazine	Clomipramine
Cimetidine hydrochloride	Molindone	Clozapine
Clorazepate	Oxcarbazepine	Darifenacin
Codeine	Pethidine hydrochloride	Desipramine
Colchicine	Pimozide	Dicyclomine
Dextropropoxyphene		Diphenhydramine
Diazepam		Doxepin
Digoxin		Flavoxate
Dipyridamole		Hydroxyzine
Disopyramide phosphate		Hyoscyamine
Fentanyl		Imipramine
Fluvoxamine		Meclizine
Furosemide		Nortriptyline
Haloperidol		Orphenadrine
Hydralazine		Oxybutynin
Hydrocortisone		Paroxetine
Isosorbide preparations		Perphenazine
Loperamide		Procyclidine
Metoprolol		Promazine
Morphine		Promethazine
Nifedipine		Propentheline
Prednisone/Prednisolone		Pyrilamine
Quinidine		Scopolamine
Ranitidine		Thioridazine (withdrawn)
Theophylline		Tolterodine
Timolol maleate		Trifluoperazine
Trazodone		Trihexyphenidyl
Triamterene		Trimipramine
Warfarin		



Drug ***withdrawal*** associated with delirium

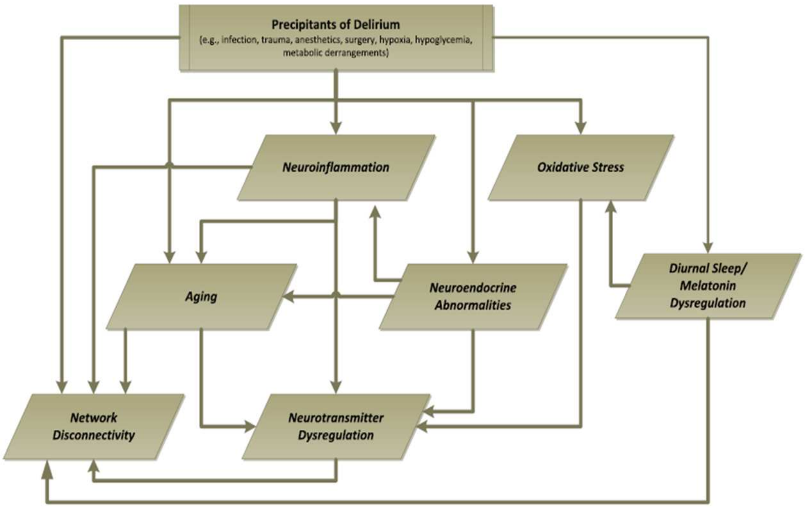
- Alcohol
- Barbiturates
- Sedative/Hypnotics
- Nicotine
- Opioids
- SSRI's

Differential diagnosis

“I WATCH DEATH”

- I Infection
- W Withdrawal (non-EtOH)
- A Acute metabolic
- T Trauma
- C Central nervous system pathology
- H Hypoxia
- D Deficiencies
- E Endocrinopathies
- A Acute vascular
- T Toxins
- H Heavy metals

Why does it happen to so many people?


Precipitants of Delirium
(e.g., infection, trauma, anesthetics, surgery, hypoxia, hypoglycemia, metabolic derrangements)
Neuroinflammation
Oxidative Stress
Aging
Neuroendocrine Abnormalities
Diurnal Sleep/ Melatonin Dysregulation
Network Disconnectivity
Neurotransmitter Dysregulation

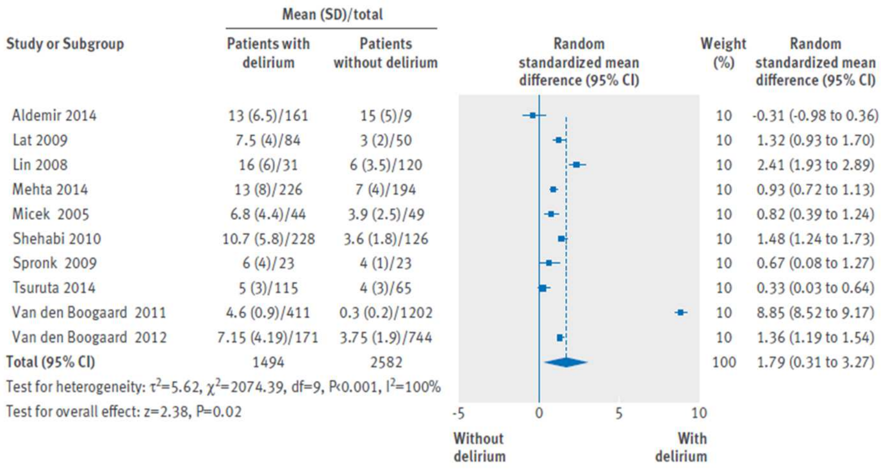
Maldonado JR. Am J Geriatr Psychiatry 2013;21:1190-1222

Consequences of delirium

- **Short term**
  - **Longer time on mechanical ventilation**
  - **Longer length of stay in the ICU and hospital**
  - **Death**

- Long term
  - Death
  - PICS (Post-ICU Syndrome)

Impact of delirium on mechanical ventilation:
Mean duration of mechanical ventilation was 1.79 days longer



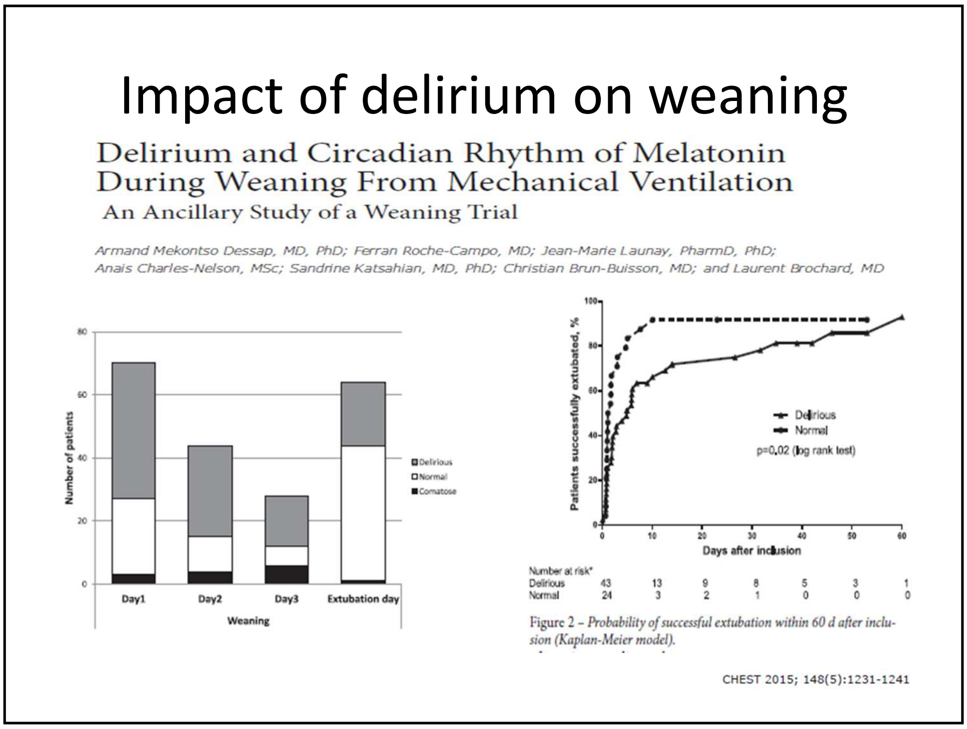
Study or Subgroup	Mean (SD)/total: Patients with delirium	Mean (SD)/total: Patients without delirium	Weight (%)	Random standardized mean difference (95% CI)
Aldemir 2014	13 (6.5)/161	15 (5)/9	10	-0.31 (-0.98 to 0.36)
Lat 2009	7.5 (4)/84	3 (2)/50	10	1.32 (0.93 to 1.70)
Lin 2008	16 (6)/31	6 (3.5)/120	10	2.41 (1.93 to 2.89)
Mehta 2014	13 (8)/226	7 (4)/194	10	0.93 (0.72 to 1.13)
Micek 2005	6.8 (4.4)/44	3.9 (2.5)/49	10	0.82 (0.39 to 1.24)
Shehabi 2010	10.7 (5.8)/228	3.6 (1.8)/126	10	1.48 (1.24 to 1.73)
Spronk 2009	6 (4)/23	4 (1)/23	10	0.67 (0.08 to 1.27)
Tsuruta 2014	5 (3)/115	4 (3)/65	10	0.33 (0.03 to 0.64)
Van den Boogaard 2011	4.6 (0.9)/411	0.3 (0.2)/1202	10	8.85 (8.52 to 9.17)
Van den Boogaard 2012	7.15 (4.19)/171	3.75 (1.9)/744	10	1.36 (1.19 to 1.54)
Total (95% CI)	1494	2582	100	1.79 (0.31 to 3.27)

Test for heterogeneity: $\tau^2=5.62$, $\chi^2=2074.39$, df=9, P<0.001, $I^2=100\%$

Test for overall effect: z=2.38, P=0.02

Impact of delirium on duration (days) of mechanical ventilation in critically ill patients

BMJ 2015;350:h2538



Impact of delirium on weaning

Delirium and Circadian Rhythm of Melatonin During Weaning From Mechanical Ventilation

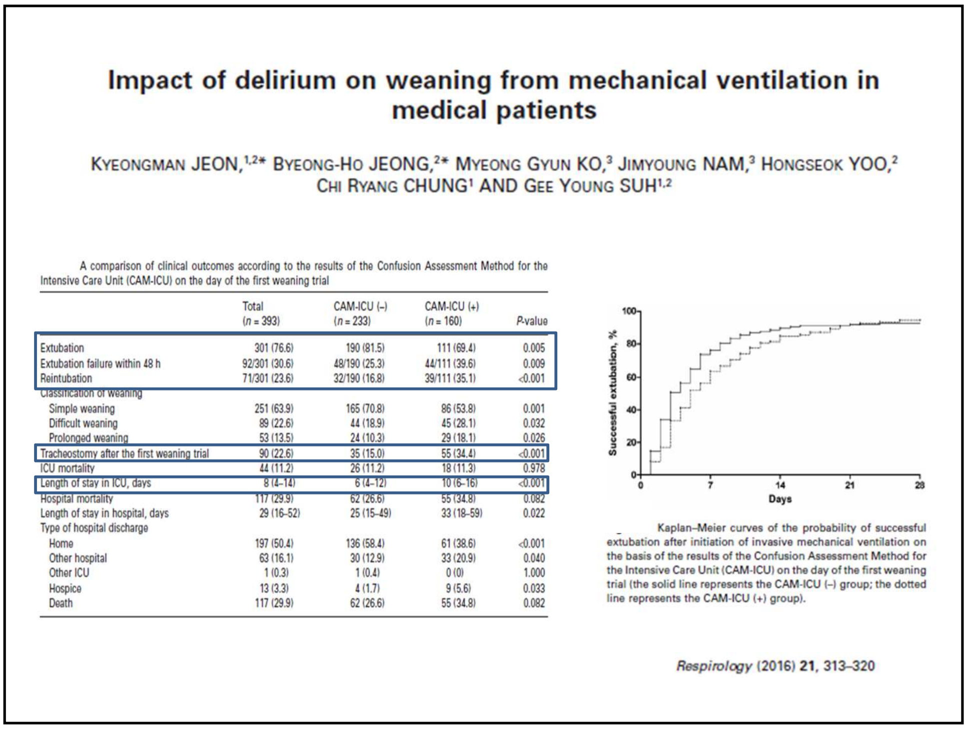
An Ancillary Study of a Weaning Trial

Armand Mekontso Dessap, MD, PhD; Ferran Roche-Campo, MD; Jean-Marie Launay, PharmD, PhD; Anais Charles-Nelson, MSc; Sandrine Katsahian, MD, PhD; Christian Brun-Buisson, MD; and Laurent Brochard, MD

Number at risk*							
Delirious	43	13	9	8	5	3	1
Normal	24	3	2	1	0	0	0

Figure 2 – *Probability of successful extubation within 60 d after inclusion (Kaplan-Meier model).*

CHEST 2015; 148(5):1231-1241



Impact of delirium on weaning from mechanical ventilation in medical patients

KYEONGMAN JEON,[1,2]* BYEONG-HO JEONG,[2]* MYEONG GYUN KO,[3] JIMYOUNG NAM,[3] HONGSEOK YOO,[2]
CHI RYANG CHUNG[1] AND GEE YOUNG SUH[1,2]

A comparison of clinical outcomes according to the results of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) on the day of the first weaning trial

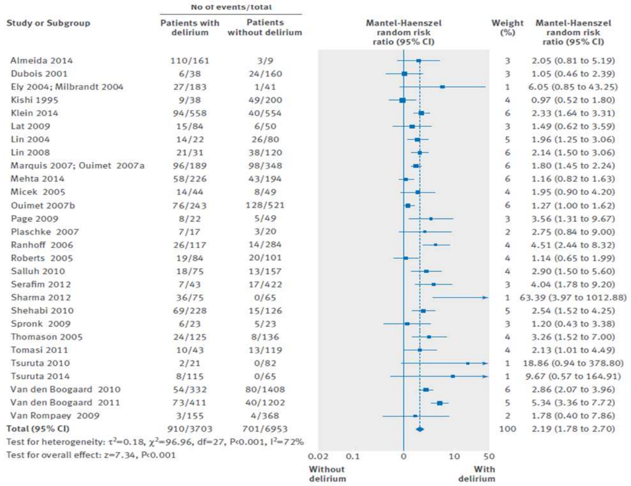
	Total (*n* = 393)	CAM-ICU (–) (*n* = 233)	CAM-ICU (+) (*n* = 160)	*P*-value
Extubation	301 (76.6)	190 (81.5)	111 (69.4)	0.005
Extubation failure within 48 h	92/301 (30.6)	48/190 (25.3)	44/111 (39.6)	0.009
Reintubation	71/301 (23.6)	32/190 (16.8)	39/111 (35.1)	<0.001
Classification of weaning				
Simple weaning	251 (63.9)	165 (70.8)	86 (53.8)	0.001
Difficult weaning	89 (22.6)	44 (18.9)	45 (28.1)	0.032
Prolonged weaning	53 (13.5)	24 (10.3)	29 (18.1)	0.026
Tracheostomy after the first weaning trial	90 (22.6)	35 (15.0)	55 (34.4)	<0.001
ICU mortality	44 (11.2)	26 (11.2)	18 (11.3)	0.978
Length of stay in ICU, days	8 (4–14)	6 (4–12)	10 (6–16)	<0.001
Hospital mortality	117 (29.9)	62 (26.6)	55 (34.8)	0.082
Length of stay in hospital, days	29 (16–52)	25 (15–49)	33 (18–59)	0.022
Type of hospital discharge				
Home	197 (50.4)	136 (58.4)	61 (38.6)	<0.001
Other hospital	63 (16.1)	30 (12.9)	33 (20.9)	0.040
Other ICU	1 (0.3)	1 (0.4)	0 (0)	1.000
Hospice	13 (3.3)	4 (1.7)	9 (5.6)	0.033
Death	117 (29.9)	62 (26.6)	55 (34.8)	0.082

Kaplan–Meier curves of the probability of successful extubation after initiation of invasive mechanical ventilation on the basis of the results of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) on the day of the first weaning trial (the solid line represents the CAM-ICU (–) group; the dotted line represents the CAM-ICU (+) group).

Respirology (2016) **21**, 313–320

Outcome of delirium in critically ill patients: systematic review and meta-analysis

Jorge I F Salluh,[1] Han Wang,[2] Eric B Schneider,[2] Neeraja Nagaraja,[2] Gayane Yenokyan,[3] Abdulla Damluji,[4] Rodrigo B Serafim,[1,5] Robert D Stevens[6]



Study or Subgroup	No of events/total: Patients with delirium	No of events/total: Patients without delirium	Weight (%)	Mantel-Haenszel random risk ratio (95% CI)
Almeida 2014	110/161	3/9	3	2.05 (0.81 to 5.19)
Dubois 2001	6/38	24/160	3	1.05 (0.46 to 2.39)
Ely 2004; Milbrandt 2004	27/183	1/41	1	6.05 (0.85 to 43.25)
Kishi 1995	9/38	49/200	4	0.97 (0.52 to 1.80)
Klein 2014	94/558	40/554	6	2.33 (1.64 to 3.31)
Lat 2009	15/84	6/50	3	1.49 (0.62 to 3.59)
Lin 2004	14/22	26/80	5	1.96 (1.25 to 3.06)
Lin 2008	21/31	38/120	6	2.14 (1.50 to 3.06)
Marquis 2007; Ouimet 2007a	96/189	98/348	6	1.80 (1.45 to 2.24)
Mehta 2014	58/226	43/194	6	1.16 (0.82 to 1.63)
Micek 2005	14/44	8/49	4	1.95 (0.90 to 4.20)
Ouimet 2007b	76/243	128/521	6	1.27 (1.00 to 1.62)
Page 2009	8/22	5/49	3	3.56 (1.31 to 9.67)
Plaschke 2007	7/17	3/20	2	2.75 (0.84 to 9.00)
Ranhoff 2006	26/117	14/284	4	4.51 (2.44 to 8.32)
Roberts 2005	19/84	20/101	4	1.14 (0.65 to 1.99)
Salluh 2010	18/75	13/157	4	2.90 (1.50 to 5.60)
Serafim 2012	7/43	17/422	3	4.04 (1.78 to 9.20)
Sharma 2012	36/75	0/65	1	63.39 (3.97 to 1012.88)
Shehabi 2010	69/228	15/126	5	2.54 (1.52 to 4.25)
Spronk 2009	6/23	5/23	3	1.20 (0.43 to 3.38)
Thomason 2005	24/125	8/136	4	3.26 (1.52 to 7.00)
Tomasi 2011	10/43	13/119	4	2.13 (1.01 to 4.49)
Tsuruta 2010	2/21	0/82	1	18.86 (0.94 to 378.80)
Tsuruta 2014	8/115	0/65	1	9.67 (0.57 to 164.91)
Van den Boogaard 2010	54/332	80/1408	6	2.86 (2.07 to 3.96)
Van den Boogaard 2011	73/411	40/1202	5	5.34 (3.36 to 7.72)
Van Rompaey 2009	3/155	4/368	2	1.78 (0.40 to 7.86)
Total (95% CI)	910/3703	701/6953	100	2.19 (1.78 to 2.70)

Test for heterogeneity: $\tau^2=0.18$, $\chi^2=96.96$, df=27, P<0.001, $I^2=72\%$

Test for overall effect: z=7.34, P<0.001

Impact of delirium on hospital mortality in critically ill patients

Impact of delirium on hospital mortality

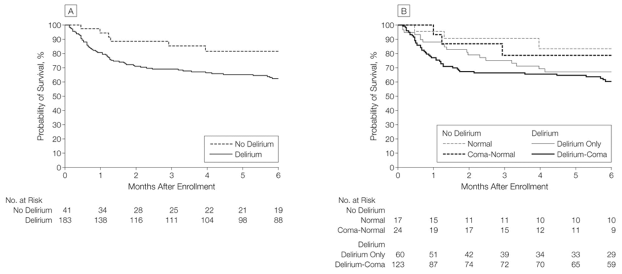
BMJ 2015;350:h2538

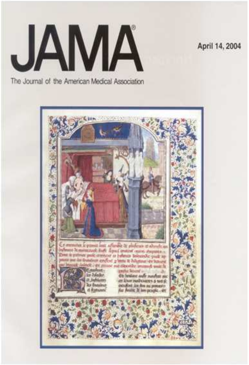
Consequences of delirium:

- Short term
  - Longer time on mechanical ventilation
  - Longer length of stay in the ICU and hospital
  - Death
- **Long term**
  - **Death**
  - **PICS (Post-ICU Syndrome)**

CARING FOR THE
CRITICALLY ILL PATIENT

Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit




JAMA
April 14, 2004
The Journal of the American Medical Association

JAMA. 2004;291:1753-1762. © American Medical Association

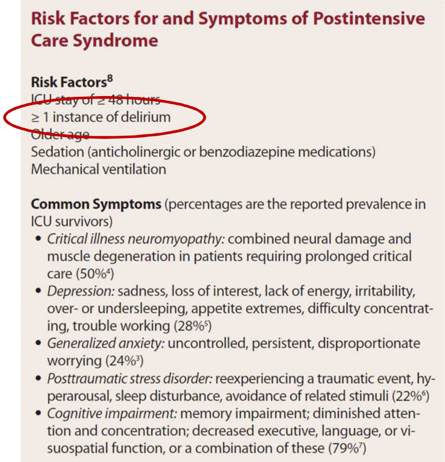
Ely EW et al, JAMA 2004;291-1753-1762

What does survivorship look like?

Alive ≠ Alive and well

Post-intensive care syndrome (PICS)

New or worsening impairment in cognition, mental health, and physical function after critical illness.



Risk Factors for and Symptoms of Postintensive Care Syndrome

Risk Factors[8]
ICU stay of ≥ 48 hours
≥ 1 instance of delirium
Older age
Sedation (anticholinergic or benzodiazepine medications)
Mechanical ventilation

Common Symptoms (percentages are the reported prevalence in ICU survivors)

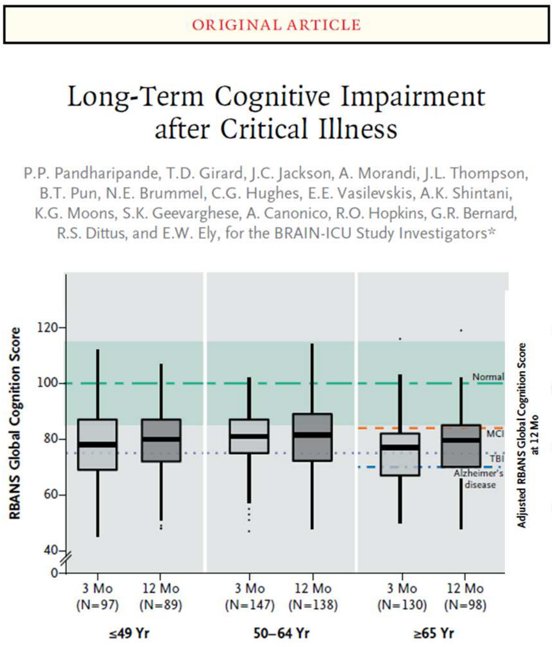
- *Critical illness neuromyopathy:* combined neural damage and muscle degeneration in patients requiring prolonged critical care (50%[4])
- *Depression:* sadness, loss of interest, lack of energy, irritability, over- or undersleeping, appetite extremes, difficulty concentrating, trouble working (28%[5])
- *Generalized anxiety:* uncontrolled, persistent, disproportionate worrying (24%[3])
- *Posttraumatic stress disorder:* reexperiencing a traumatic event, hyperarousal, sleep disturbance, avoidance of related stimuli (22%[6])
- *Cognitive impairment:* memory impairment; diminished attention and concentration; decreased executive, language, or visuospatial function, or a combination of these (79%[7])

AJN 2015;115:24-31

Post-ICU Syndrome

- **At discharge**
  - **46-80% cognitive impaired**
- **At 3 and 12 M**
  - **40% and 34% comparable to moderate TBI**
- **At 12M**
  - **20-30% anxiety, PTSD,depression**
  - **27% functional impairment (affecting ADL and other activities such as medication and finance management)**

Other: sexual dysfunction, inability to return to work, chronic pain, etc.



ORIGINAL ARTICLE

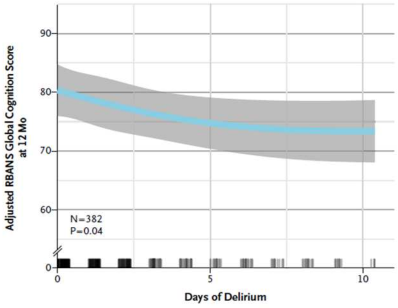
Long-Term Cognitive Impairment after Critical Illness

P.P. Pandharipande, T.D. Girard, J.C. Jackson, A. Morandi, J.L. Thompson, B.T. Pun, N.E. Brummel, C.G. Hughes, E.E. Vasilevskis, A.K. Shintani, K.G. Moons, S.K. Geevarghese, A. Canonico, R.O. Hopkins, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the BRAIN-ICU Study Investigators*

Patients admitted to medical or surgical ICU for respiratory failure or shock.

3M: 40% scored c/w mod TBI; 26% c/w mild Alzheimer

Impairment at 3 and 12 M not consistently associated with sedation



N Engl J Med 2013; 369:1306-1316

Post-ICU Syndrome

64.3% of the patients were diagnosed with delirium during their ICU stay

Nineteen of the 28 patients *not diagnosed with delirium* still had clear memories of delusions.

In all, 84 patients out of the 101 (83.2%) had signs indicating acute brain dysfunction during their ICU stay.

Dan Med J 2015;62:A5062

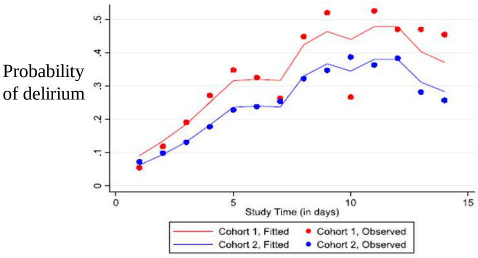
Principles of delirium treatment

- **Four P's:**
  - **PREVENTION**
  - **PREVENTION**
  - **PREVENTION**
  - **Psychotropics**
  - **Not Polypharmacy!!!**

Improved Analgesia, Sedation, and Delirium Protocol Associated with Decreased Duration of Delirium and Mechanical Ventilation

Christopher R. Dale[1], Delores A. Kannas[2], Vincent S. Fan[3], Stephen L. Daniel[4], Steven Deem[5], N. David Yanez III[4], Catherine L. Hough[1], Timothy H. Dellit[6], and Miriam M. Treggiari[5]

	Baseline (*n* = *703*)	Sedation-Reducing (*n* = *780*)	*P* Value*
Discharged alive, n (%)	607 (86.3)	673 (86.3)	1.0
Discharged home, n (%)	373 (53.1)	386 (49.6)	0.2
Discharged to SNF only, n (%)	146 (20.8)	161 (20.6)	1.0
Discharged to SNF, LTAC, or other institution, n (%)	230 (32.7)	282 (36.2)	0.2
28-day ventilator-free survival, median (IQR), d	25 (17–26)	26 (20–26)	<0.01
Duration of mechanical ventilation, median (IQR), h	20 (7–61)	16 (6–44)	0.01
Duration of ICU stay, median (IQR), d	3 (1–7)	3 (1–6)	0.03
Duration of hospitalization, median (IQR), d	11 (5–21)	10 (4–18)	0.02
VAP, n (%)	46 (6.5)	36 (4.6)	0.08
VAP rate (n/1,000 ventilator-days), mean (SD)	11.7 (16.7)	9.7 (16.3)	0.40



AnnalsATS Volume 11 Number 3 | March 2014

Effectiveness and Safety of the Awakening and Breathing Coordination, Delirium Monitoring/ Management, and Early Exercise/Mobility Bundle*

Michele C. Balas, PhD, RN, APRN-NP, CCRN[1]; Eduard E. Vasilevskis, MD, MPH[2,3,4];
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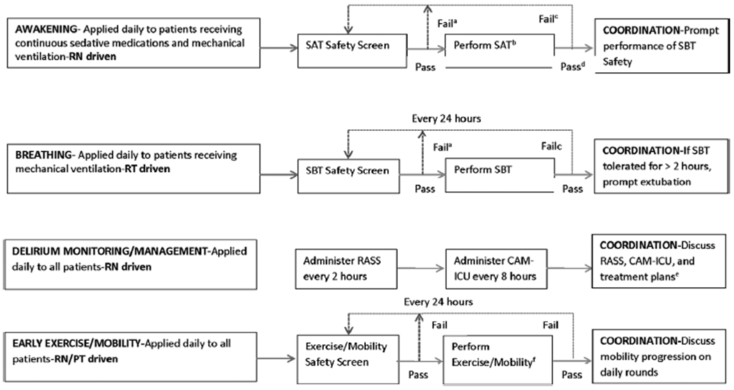
Marlene Z. Cohen, PhD, RN, FAAN[8]; Gregory Peitz, PharmD, BCPS[5,6];
David E. Gannon, MD, FACP, FCCP[9]; Joseph Sisson, MD[9]; James Sullivan, MD[10];
Joseph C. Stothert, MD, PhD, FCCM, FACS[11]; Julie Lazure, BSN, RN[12]; Suzanne L. Nuss, PhD, RN[13];
Randeep S. Jawa, MD, FACS, FCCM[11]; Frank Freihaut, RRT[14]; E. Wesley Ely, MD, MPH, FCCM[3,4,15];
William J. Burke, MD[16]



AWAKENING- Applied daily to patients receiving continuous sedative medications and mechanical ventilation-**RN driven**

SAT Safety Screen

Fail[a]

Perform SAT[b]

Fail[c]

Pass

Pass[d]

COORDINATION-Prompt performance of SBT Safety

Every 24 hours

BREATHING- Applied daily to patients receiving mechanical ventilation-**RT driven**

SBT Safety Screen

Fail[a]

Perform SBT

Failc

Pass

Pass

COORDINATION-If SBT tolerated for > 2 hours, prompt extubation

DELIRIUM MONITORING/MANAGEMENT-Applied daily to all patients-**RN driven**

Administer RASS every 2 hours

Administer CAM-ICU every 8 hours

COORDINATION-Discuss RASS, CAM-ICU, and treatment plans[e]

Every 24 hours

EARLY EXERCISE/MOBILITY-Applied daily to all patients-**RN/PT driven**

Exercise/Mobility Safety Screen

Fail

Perform Exercise/Mobility[f]

Fail

Pass

Pass

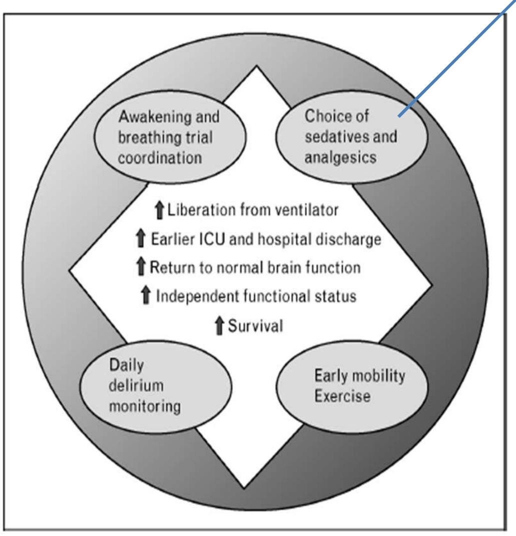
COORDINATION-Discuss mobility progression on daily rounds

Crit Care Med 2014;42:1024-1036

Effectiveness Outcomes of ABCDE Bundle Implementation

ABCDE Bundle Component Outcome	Pre-ABCDE Bundle (*n* = 146)	Post-ABCDE Bundle (*n* = 150)	Unadjusted *p*	Adjusted Odds Ratio	Adjusted *p*
Awakening and breathing coordination[a]					
Ventilator-free days[a]					
Mean (SD)	15 (11.4)	18 (10.6)			
Median (IQR)	21 (0–25)	24 (7–26)	0.04		
Delirium monitoring/management					
Delirium anytime, *n* (%)	91 (62.3)	73 (48.7)	0.02	0.55[b] (0.33–0.93)	0.03
Duration of delirium, days, median (IQR)	3 (1–6)	2 (1–4)	0.52		
Percent ICU days spent delirious, median (IQR)	50 (30–64.3)	33.3 (18.8–50)	0.003		
Coma anytime, *n* (%)	41 (28.1)	43 (28.7)	0.91	1.00[b]	0.99
Coma days, median (IQR)	2 (1–4)	2 (1–5)	0.35		
Percent ICU days spent in coma, median (IQR)	25 (18.2–44.4)	25 (12.5–42.9)	0.89		
Richmond Agitation-Sedation Scale Score, mean (SD)	0.02 (1.4)	−1.03 (1.2)	0.38		

Crit Care Med 2014;42:1024-1036


Awakening and breathing trial coordination
Choice of sedatives and analgesics
↑ Liberation from ventilator
↑ Earlier ICU and hospital discharge
↑ Return to normal brain function
↑ Independent functional status
↑ Survival
Daily delirium monitoring
Early mobility Exercise

Curr Opin Crit Care 17:43–49

Analgosedation of choice per ICU Liberation protocol: fentanyl infusion

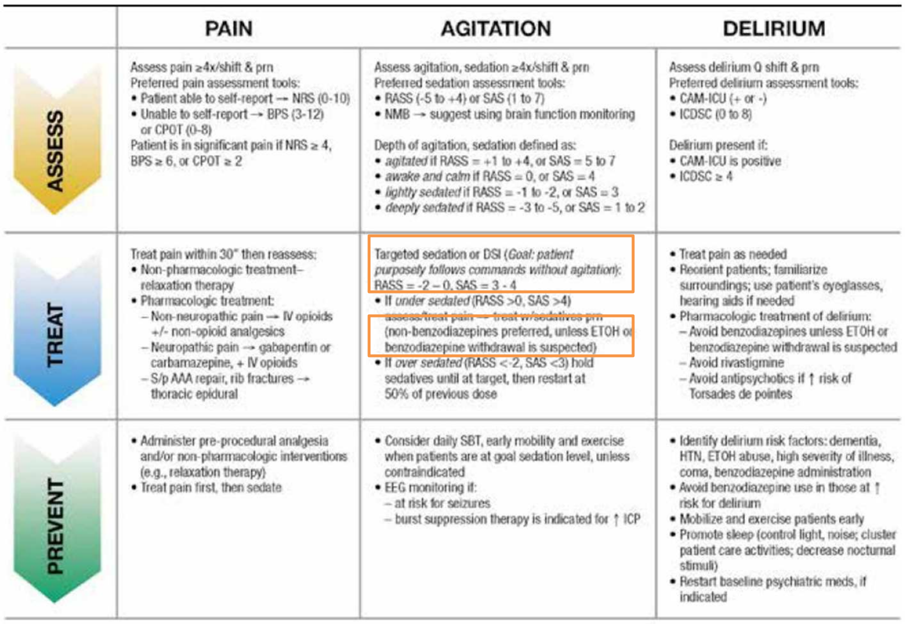
Routine benzodiazepine use is discouraged per PAD-guidelines

If continuous sedation is required, dexmedetomidine has advantages

Regardless of the choice of sedative, avoid "too much for too long" by targeted sedation or daily interruption.

Don't forget non-pharmacologic strategies:
-Sleep promotion
-Music therapy
-Early mobilization
-Access to family and assisted communication

Figure 1: The ICU PAD Care Bundle



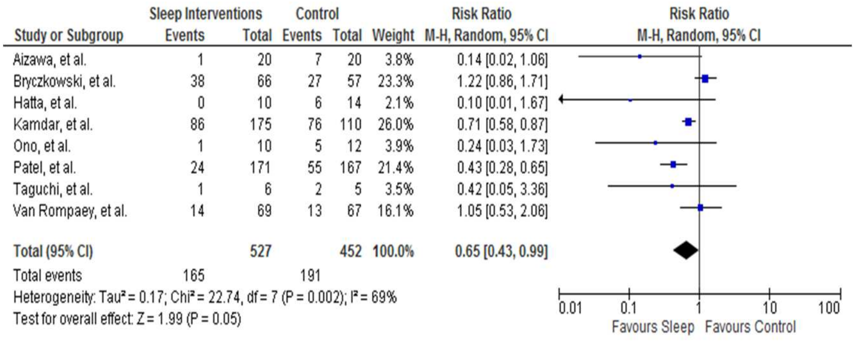
	PAIN	AGITATION	DELIRIUM
ASSESS	Assess pain ≥4x/shift & prn Preferred pain assessment tools: • Patient able to self-report → NRS (0-10) • Unable to self-report → BPS (3-12) or CPOT (0-8) Patient is in significant pain if NRS ≥ 4, BPS ≥ 6, or CPOT ≥ 2	Assess agitation, sedation ≥4x/shift & prn Preferred sedation assessment tools: • RASS (-5 to +4) or SAS (1 to 7) • NMB → suggest using brain function monitoring Depth of agitation, sedation defined as: • *agitated* if RASS = +1 to +4, or SAS = 5 to 7 • *awake and calm* if RASS = 0, or SAS = 4 • *lightly sedated* if RASS = -1 to -2, or SAS = 3 • *deeply sedated* if RASS = -3 to -5, or SAS = 1 to 2	Assess delirium Q shift & prn Preferred delirium assessment tools: • CAM-ICU (+ or -) • ICDSC (0 to 8) Delirium present if: • CAM-ICU is positive • ICDSC ≥ 4
TREAT	Treat pain within 30" then reassess: • Non-pharmacologic treatment–relaxation therapy • Pharmacologic treatment: – Non-neuropathic pain → IV opioids +/- non-opioid analgesics – Neuropathic pain → gabapentin or carbamazepine, + IV opioids – S/p AAA repair, rib fractures → thoracic epidural	Targeted sedation or DSI (*Goal: patient purposely follows commands without agitation*): RASS = -2 – 0, SAS = 3 - 4 • If *under sedated* (RASS >0, SAS >4) ~~assess/treat pain → treat w/sedatives prn~~ (non-benzodiazepines preferred, unless ETOH or benzodiazepine withdrawal is suspected) • If *over sedated* (RASS <-2, SAS <3) hold sedatives until at target, then restart at 50% of previous dose	• Treat pain as needed • Reorient patients; familiarize surroundings; use patient's eyeglasses, hearing aids if needed • Pharmacologic treatment of delirium: – Avoid benzodiazepines unless ETOH or benzodiazepine withdrawal is suspected – Avoid rivastigmine – Avoid antipsychotics if ↑ risk of Torsades de pointes
PREVENT	• Administer pre-procedural analgesia and/or non-pharmacologic interventions (e.g., relaxation therapy) • Treat pain first, then sedate	• Consider daily SBT, early mobility and exercise when patients are at goal sedation level, unless contraindicated • EEG monitoring if: – at risk for seizures – burst suppression therapy is indicated for ↑ ICP	• Identify delirium risk factors: dementia, HTN, ETOH abuse, high severity of illness, coma, benzodiazepine administration • Avoid benzodiazepine use in those at ↑ risk for delirium • Mobilize and exercise patients early • Promote sleep (control light, noise; cluster patient care activities; decrease nocturnal stimuli) • Restart baseline psychiatric meds, if indicated

Adapted with permission. © 2013. Wolters Kluwer Health. Barr J, Fraser GL, Puntillo K, et al. Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the ICU. *Crit Care Med.* 2013; 1:263-306.

Sleep and sedation

- Sleep is; sedation is not
  - Essential
  - Circadian
  - Continuous/consolidated in one period of time
  - Characterized by cycling sleep stages

Sleep interventions to prevent delirium: A systematic review



	Sleep Interventions		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Aizawa, et al.	1	20	7	20	3.8%	0.14 [0.02, 1.06]
Bryczkowski, et al.	38	66	27	57	23.3%	1.22 [0.86, 1.71]
Hatta, et al.	0	10	6	14	2.1%	0.10 [0.01, 1.67]
Kamdar, et al.	86	175	76	110	26.0%	0.71 [0.58, 0.87]
Ono, et al.	1	10	5	12	3.9%	0.24 [0.03, 1.73]
Patel, et al.	24	171	55	167	21.4%	0.43 [0.28, 0.65]
Taguchi, et al.	1	6	2	5	3.5%	0.42 [0.05, 3.36]
Van Rompaey, et al.	14	69	13	67	16.1%	1.05 [0.53, 2.06]
Total (95% CI)		**527**		**452**	**100.0%**	**0.65 [0.43, 0.99]**
Total events	165		191			

Heterogeneity: Tau² = 0.17; Chi² = 22.74, df = 7 (P = 0.002); I² = 69%

Test for overall effect: Z = 1.99 (P = 0.05)

Flannery et al. Crit Care Med 2016

Take home messages

- Delirium is common especially in older, sicker patients.
- Some cases of delirium are iatrogenic; choice of medication, especially analgosedation is very important
- Delirium is associated with longer length of stay, longer length of time on mechanical ventilation, and death in the short term and death and PICS in the long term

There is no “treatment” that is known to affect the course or outcomes once delirium has been diagnosed

- Prevention is the key
  - Following evidence-based guidelines for Pain,Agitation, Delirium and the ABCDE(F) bundle

Question #1

- A 56 yo man with hypertension and diabetes is admitted for sepsis. He is intubated, sedated with a midazolam infusion, and treated with broad spectrum antibiotics. On ICU day 3 his cultures confirm that he has a Legionella pneumonia so his antibiotics are de-escalated. On day 7 he is hemodynamically stable, his midazolam infusion is stopped, and he passed a spontaneous breathing trial. Extubation is considered but he is uncooperative and belligerent. Which of the following is true:

- A. He needs a head CT to rule out a stroke or CNS abscess
- B. His antibiotics were de-escalated too soon
- C. He is most likely delirious from the lasting effect of midazolam even though it has a short half-life
- D. You should tell his family that his mental status will be back to normal by the time he is discharged home

Answer: Question #1

Which of the following is true?

- A. He needs a head CT to rule out a stroke or CNS abscess
- B. His antibiotics were de-escalated too soon
- **C. He is most likely delirious from the lasting effect of midazolam even though it has a short half-life**
- D. You should tell his family that his mental status will be back to normal by the time he is discharged home

Question #2

- The patient in question #1 is extubated and transferred to a rehabilitation facility for 2 weeks before returning home. He is able to return to his job as a supervisor at a clothing factory several weeks later. He presents for a follow-up appointment with his primary care provider 2 months after discharge home. He tells you that he has memories of the nurses trying to kill him in the ICU and he is having trouble sleeping. Which of the following is true?:

- A. It would not be surprising if he has cognitive problems that were not present prior to admission.
- B. His delusional memories suggest that he is having a psychotic episode and he should be re-hospitalized.
- C. If he had been given more midazolam during his hospitalization he would not have delusional memories and he would be less likely to have post-traumatic stress syndrome (PTSD).
- D. At this point, so far removed from his hospitalization, his sleep and memory problems must be something that newly developed after discharge.

Answer: Question #2

Which of the following is true?:

- **A. It would not be surprising if he has cognitive problems that were not present prior to admission.**
- B. His delusional memories suggest that he is having a psychotic episode and he should be re-hospitalized.
- C. If he had been given more midazolam during his hospitalization he would not have delusional memories and he would be less likely to have post-traumatic stress syndrome (PTSD).
- D. At this point, so far removed from his hospitalization, his sleep and memory problems must be something that newly developed after discharge.

References

- JAMA 2004;291-1753-1762
- NEJM 2013; 369:1306-1316
- Crit Care Med 2014;42:1024-1036
- Crit Car Med 2013;1:263-306

BRIGHAM AND
WOMEN'S HOSPITAL
| The Lung Center |

Harvard
Medical School

ICU Issues for the Transplant Recipient

Hilary J. Goldberg, MD, MPH
Medical Director, Lung Transplant Program
QAPI Physician Lead
Brigham and Women's Hospital

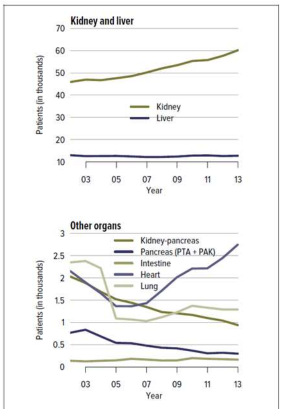
Disclosures

- Reports no commercial interest

Overview

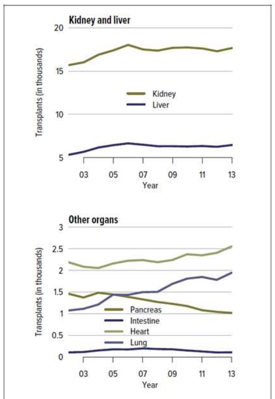
- Background
- Underlying disease/comorbidities
- Donor issues
- Common things are common
- Technical Issues
- Infection
- Immunologic concerns
- Medication side effects

Background



INT 1 Candidates active on the waiting list on December 31 of the year

Patients concurrently listed at multiple centers are counted once. Those with concurrent listings and active at any program are considered active. PAK, pancreas after kidney; PTA, pancreas transplant alone.



INT 3 Total transplants, adult and pediatric

Kidney: patients undergoing kidney or simultaneous pancreas-kidney (SPK) transplant. Pancreas: patients undergoing pancreas or SPK transplant. Heart: patients undergoing heart or heart-lung transplant. Lung: patients undergoing lung or heart-lung transplant. Retransplants and multi-organ transplants are included.

Am J Transp 2015; 15:8

Background

Evolution in Transplantation
- Liberalized acceptance criteria for donor and recipient
- Increasing acceptable age of donors and recipients
- Evolving allocation systems – prioritize patients in most urgent need
- Mechanical circulatory support, "bridge to transplant"

Result
- Increasing likelihood of ICU stay before and after transplantation
- More complex medical issues during ICU stay
- Need for comprehensive, multidisciplinary approach to care
- Need for ongoing QAPI

Pre-existing Disease/Comorbidities

- Liberalization of acceptance in setting of medical comorbidities
- Impact of secondary organ dysfunction on allocation – e.g. – renal dysfunction
- Thoracic Transplantation – pulmonary HTN, right heart dysfunction

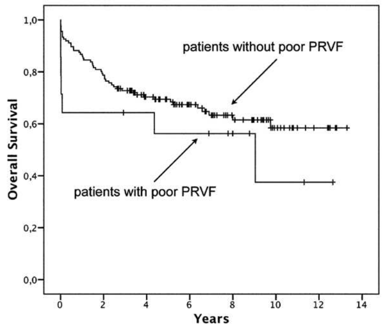
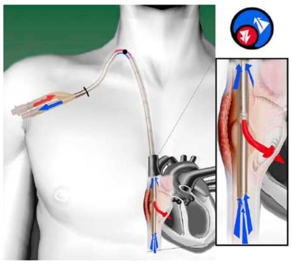


Fig. 1. Cumulative survival of lung transplant patients with or without poor preoperative right-ventricular function (PRVF).

Eur J CT Surg 2011; 39: 538

Mechanical Circulatory Support/Bridge to Transplant



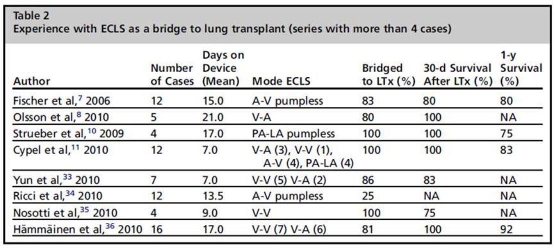


Table 2
Experience with ECLS as a bridge to lung transplant (series with more than 4 cases)

Author	Number of Cases	Days on Device (Mean)	Mode ECLS	Bridged to LTx (%)	30-d Survival After LTx (%)	1-y Survival (%)
Fischer et al,[7] 2006	12	15.0	A-V pumpless	83	80	80
Olsson et al,[8] 2010	5	21.0	V-A	80	100	NA
Strueber et al,[10] 2009	4	17.0	PA-LA pumpless	100	100	75
Cypel et al,[11] 2010	12	7.0	V-A (3), V-V (1), A-V (4), PA-LA (4)	100	100	83
Yun et al,[33] 2010	7	7.0	V-V (5) V-A (2)	86	83	NA
Ricci et al,[34] 2010	12	13.5	A-V pumpless	25	NA	NA
Nosotti et al,[35] 2010	4	9.0	V-V	100	75	NA
Hämmäinen et al,[36] 2010	16	17.0	V-V (7) V-A (6)	81	100	92

Clin Chest Med 2011; 32: 245

“Standard” Donor Criteria

- Age < 55
- ABO compatibility
- Clear CXR
- PaO2 >/= 300 mm Hg on FIO2 100%, PEEP 5 cm H2O
- </= 20 py smoking
- Absence of chest trauma
- No aspiration or sepsis
- No prior cardio-pulmonary surgery
- Gram stain negative for organisms
- Absence of purulent secretions on bronch

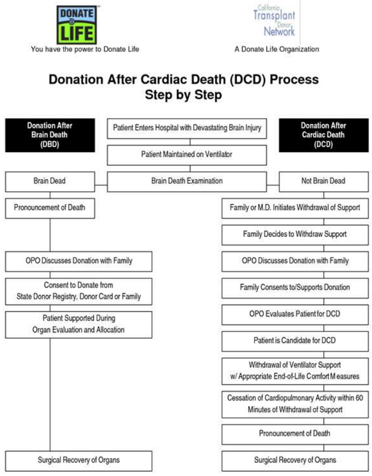
Consensus Report ISHLT, JHLT, 11/03

“Extended” Donor Criteria

- Age < 65
- No proven impairments after tob > 20 py
- No parenchymal destruction after chest trauma
- **Unilateral infiltrate, aspiration, trauma – use of contralateral lung**
- Reduced arterial oxygenation – evaluation of potential non-pulmonary cause
- Active donor management

Aigner, et al, Chest Surg Clin N. Am. 2003

Donation after cardiac death

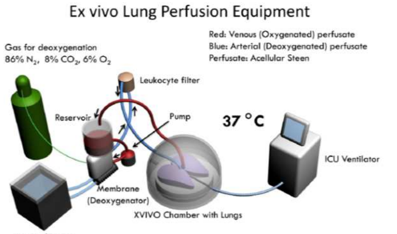

DONATE LIFE
You have the power to Donate Life
California Transplant Donor Network
A Donate Life Organization

Donation After Cardiac Death (DCD) Process
Step by Step

Donation After Brain Death (DBD)
Patient Enters Hospital with Devastating Brain Injury
Donation After Cardiac Death (DCD)
Patient Maintained on Ventilator
Brain Dead
Brain Death Examination
Not Brain Dead
Pronouncement of Death
Family or M.D. Initiates Withdrawal of Support
Family Decides to Withdraw Support
OPO Discusses Donation with Family
OPO Discusses Donation with Family
Consent to Donate from State Donor Registry, Donor Card or Family
Family Consents to/Supports Donation
Patient Supported During Organ Evaluation and Allocation
OPO Evaluates Patient for DCD
Patient is Candidate for DCD
Withdrawal of Ventilator Support w/ Appropriate End-of-Life Comfort Measures
Cessation of Cardiopulmonary Activity within 60 Minutes of Withdrawal of Support
Pronouncement of Death
Surgical Recovery of Organs
Surgical Recovery of Organs

Warm ischemia

Ex vivo lung perfusion


Ex vivo Lung Perfusion Equipment
Red: Venous (Oxygenated) perfusate
Blue: Arterial (Deoxygenated) perfusate
Perfusate: Acellular Steen
Gas for deoxygenation
86% N_2, 8% CO_2, 6% O_2
Leukocyte filter
Reservoir
Pump
37 °C
ICU Ventilator
Membrane
(Deoxygenator)
XVIVO Chamber with Lungs
Heater/Cooler

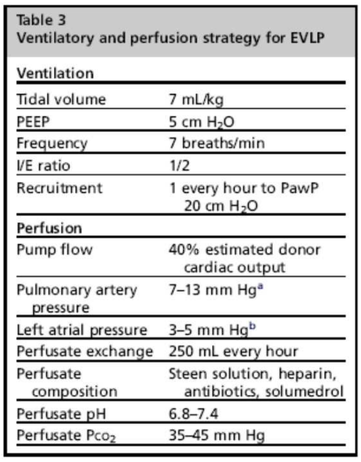


Table 3
Ventilatory and perfusion strategy for EVLP

Ventilation	
Tidal volume	7 mL/kg
PEEP	5 cm H_2O
Frequency	7 breaths/min
I/E ratio	1/2
Recruitment	1 every hour to PawP 20 cm H_2O
Perfusion	
Pump flow	40% estimated donor cardiac output
Pulmonary artery pressure	7–13 mm Hg[a]
Left atrial pressure	3–5 mm Hg[b]
Perfusate exchange	250 mL every hour
Perfusate composition	Steen solution, heparin, antibiotics, solumedrol
Perfusate pH	6.8–7.4
Perfusate Pco_2	35–45 mm Hg

Clin Chest Med 2011; 32: 233-44

Ex vivo lung perfusion

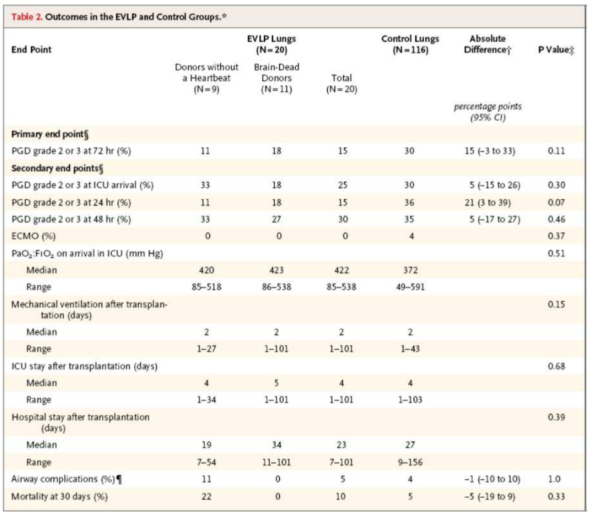


Table 2. Outcomes in the EVLP and Control Groups.*

End Point	EVLP Lungs (N=20)			Control Lungs (N=116)	Absolute Difference†	P Value‡
	Donors without a Heartbeat (N=9)	Brain-Dead Donors (N=11)	Total (N=20)		*percentage points (95% CI)*	
Primary end point§						
PGD grade 2 or 3 at 72 hr (%)	11	18	15	30	15 (−3 to 33)	0.11
Secondary end points§						
PGD grade 2 or 3 at ICU arrival (%)	33	18	25	30	5 (−15 to 26)	0.30
PGD grade 2 or 3 at 24 hr (%)	11	18	15	36	21 (3 to 39)	0.07
PGD grade 2 or 3 at 48 hr (%)	33	27	30	35	5 (−17 to 27)	0.46
ECMO (%)	0	0	0	4		0.37
PaO_2:FiO_2 on arrival in ICU (mm Hg)						0.51
Median	420	423	422	372		
Range	85–518	86–538	85–538	49–591		
Mechanical ventilation after transplantation (days)						0.15
Median	2	2	2	2		
Range	1–27	1–101	1–101	1–43		
ICU stay after transplantation (days)						0.68
Median	4	5	4	4		
Range	1–34	1–101	1–101	1–103		
Hospital stay after transplantation (days)						0.39
Median	19	34	23	27		
Range	7–54	11–101	7–101	9–156		
Airway complications (%)¶	11	0	5	4	−1 (−10 to 10)	1.0
Mortality at 30 days (%)	22	0	10	5	−5 (−19 to 9)	0.33

N Engl J Med 2011; 364: 1431-40

ICU Care – Common Things are Common

- Standard Ventilator Approach:
  - low tidal volume ventilation
  - approach to weaning
- Protocols/Bundles:
  - sedation/delirium
  - aspiration/VAP
  - VTE prophylaxis
  - decubitus ulcer prevention
  - etc
- Post-operative Fever:
  - VAP
  - CLABSI
  - CAUTI
  - acalculous cholecystitis
  - decubitus ulcer

Common things may be more common

- Transplant Recipients more susceptible to complications of hemodynamic instability
  - Pre-existing organ dysfunction
  - Prior exposure to nephrotoxins
  - Effects of immune suppression
- Capillary leak, volume overload, compartment syndrome
- Open wounds

Venous Thromboembolism

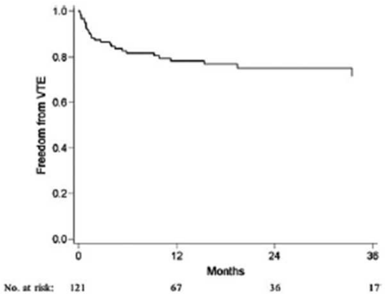


FIGURE 1. Kaplan-Meier estimate of the time to VTE.

- Risk factors:
  - Older age
  - Diabetes
  - Pneumonia
  - IPF
  - LAS era
  - Use of ECMO
  - Cumulative ICU days

Chest 2007; 132: 547
Am J Respir Crit Care Med 2013; 187:A1469

BWH Experience

- > 30% incidence of VTA
  - Majority DVT
  - Majority provoked
  - Includes fatal PE
- Identify candidates with a history of DVT/PE
- Plan for post-transplant management e discussed at the presentation of the candidate to the multidisciplinary team for listing.
- Consultation with cardiology and/or the VTE service obtained as needed
- Default choice for DVT prophylaxis in transplant recipients changed to low molecular weight heparin
- Initiate prophylaxis within 6 hours of skin closure
- Transplant recipients continue on prophylaxis at least through their one month post-transplant surveillance bronchoscopy

Early Complications

- Primary Graft Dysfunction (Re-implantation edema)
- (hyper) Acute rejection
- Bleeding
- Infection
- Airway dehiscence
- Diaphragmatic dysfunction
  - Phrenic nerve injury
- Vocal cord paralysis
- Gastric hypomotility
  - Aspiration
- Torsion

Anatomic Issues

- Anastomotic stenosis
- Outflow tract obstruction
- Dehisence/leak
- Torsion

- Etiologies:
  - Technical
  - Disrupted blood supply
  - Infection

- Management:
  - Interventional
  - Surgical

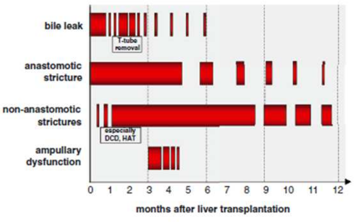
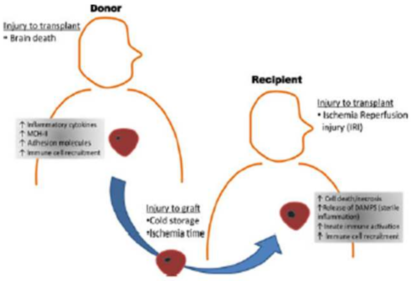


Figure 1: Typical manifestation period of different biliary complications.

Am J Trans 2013; 13: 253

Primary Graft Dysfunction


Donor
Injury to transplant
• Brain death
↑ Inflammatory cytokines
↑ MCH-II
↑ Adhesion molecules
↑ Immune cell recruitment
Injury to graft
•Cold storage
•Ischemia time
Recipient
Injury to transplant
• Ischemia Reperfusion injury (IRI)
↑ Cell death/necrosis
↑ Release of DAMPS (sterile inflammation)
↑ Innate immune activation
↑ Immune cell recruitment

- "Ischemia Reperfusion Injury"
- Result of ischemia to organ (warm and cold) followed by reperfusion
- Results in early allograft dysfunction

Immunol Rev 2014; 258: 132

Primary Graft Dysfunction

- Diagnosis of exclusion
- Grading/staging systems
- Treatment: supportive
- Avoid secondary allograft injury

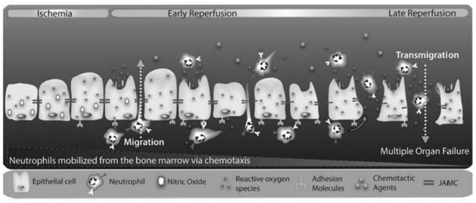
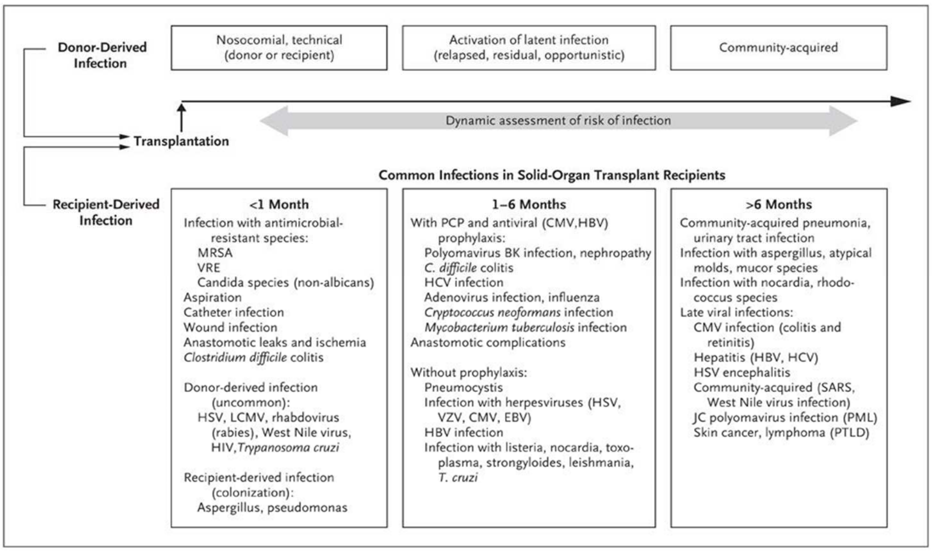

Ischemia
Early Reperfusion
Late Reperfusion
Transmigration
Migration
Multiple Organ Failure
Neutrophils mobilized from the bone marrow via chemotaxis
Epithelial cell
Neutrophil
Nitric Oxide
Reactive oxygen species
Adhesion Molecules
Chemotactic Agents
JAMC

FIG. 3. **Neutrophil migration is initiated by various chemotactic agents produced at the site of IR.** Neutrophils produce ROS and inadvertently destroy local endothelial or epithelial cells that were unaffected by the initial IR insult. JAMC is disrupted by neutrophil proteases and cell disruption, enabling neutrophils to transmigrate out of the tissue (reverse migration). Neutrophils become more resilient to apoptosis and gain enhanced ROS production, where they can now migrate to other organs and destroy tissues through ROS production leading to ARDS, SIRS, or MOF.

Shock, 2013; 40: 463

Post-transplant Infections


Donor-Derived Infection
Nosocomial, technical (donor or recipient)
Activation of latent infection (relapsed, residual, opportunistic)
Community-acquired
Transplantation
Dynamic assessment of risk of infection
Recipient-Derived Infection

Common Infections in Solid-Organ Transplant Recipients

<1 Month

Infection with antimicrobial-resistant species:
  MRSA
  VRE
  Candida species (non-albicans)
Aspiration
Catheter infection
Wound infection
Anastomotic leaks and ischemia
Clostridium difficile colitis

Donor-derived infection (uncommon):
  HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, *Trypanosoma cruzi*

Recipient-derived infection (colonization):
  Aspergillus, pseudomonas

1–6 Months

With PCP and antiviral (CMV,HBV) prophylaxis:
  Polyomavirus BK infection, nephropathy
  C. difficile colitis
  HCV infection
  Adenovirus infection, influenza
  Cryptococcus neoformans infection
  Mycobacterium tuberculosis infection
Anastomotic complications

Without prophylaxis:
  Pneumocystis
  Infection with herpesviruses (HSV, VZV, CMV, EBV)
  HBV infection
  Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, *T. cruzi*

>6 Months

Community-acquired pneumonia, urinary tract infection
Infection with aspergillus, atypical molds, mucor species
Infection with nocardia, rhodococcus species
Late viral infections:
  CMV infection (colitis and retinitis)
  Hepatitis (HBV, HCV)
  HSV encephalitis
  Community-acquired (SARS, West Nile virus infection)
  JC polyomavirus infection (PML)
  Skin cancer, lymphoma (PTLD)

Peri-Operative Management

- Antibiotics: Empiric, tailored to risk of infection and center’s
- Anti-virals: Valgancyclovir or valacyclovir
- Antifungals: Organ/program specific
- Pneumocystis:
  - Bactrim – start when counts and renal function stable
- (Toxoplasma positive recipients:
  - daily Bactrim)

Peri-Operative Infections

- Common things are common
  - UTI
  - CLABSI
  - Wound infection
  - VAP
  - Hospital acquired infection
  - C. diff
    - Association with low IgG

Risk of CMV Complications

High

- Donor positive/Recipient negative

- Donor positive/recipient positive
- Donor negative/recipient positive

- Donor negative/recipient negative

↓

Low

Extended Antiviral Prophylaxis

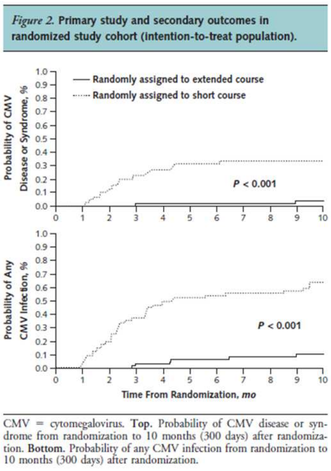


Figure 2. **Primary study and secondary outcomes in randomized study cohort (intention-to-treat population).**

CMV = cytomegalovirus. **Top.** Probability of CMV disease or syndrome from randomization to 10 months (300 days) after randomization. **Bottom.** Probability of any CMV infection from randomization to 10 months (300 days) after randomization.

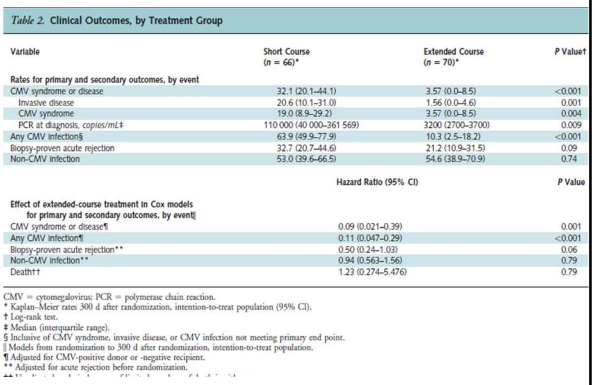


Table 2. **Clinical Outcomes, by Treatment Group**

Variable	Short Course (n = 66)*	Extended Course (n = 70)*	P Value†
Rates for primary and secondary outcomes, by event			
CMV syndrome or disease	32.1 (20.1–44.1)	3.57 (0.0–8.5)	<0.001
Invasive disease	20.6 (10.1–31.0)	1.56 (0.0–4.6)	0.001
CMV syndrome	19.0 (8.9–29.2)	3.57 (0.0–8.5)	0.004
PCR at diagnosis, *copies/mL*‡	110 000 (40 000–361 569)	3200 (2700–3700)	0.009
Any CMV infection§	63.9 (49.9–77.9)	10.3 (2.5–18.2)	<0.001
Biopsy-proven acute rejection	32.7 (20.7–44.6)	21.2 (10.9–31.5)	0.09
Non-CMV infection	53.0 (39.6–66.5)	54.6 (38.9–70.9)	0.74

	Hazard Ratio (95% CI)	P Value
Effect of extended-course treatment in Cox models for primary and secondary outcomes, by event‖		
CMV syndrome or disease¶	0.09 (0.021–0.39)	0.001
Any CMV infection¶	0.11 (0.047–0.29)	<0.001
Biopsy-proven acute rejection**	0.50 (0.24–1.03)	0.06
Non-CMV infection**	0.94 (0.563–1.56)	0.79
Death††	1.23 (0.274–5.476)	0.79

CMV = cytomegalovirus; PCR = polymerase chain reaction.
* Kaplan–Meier rates 300 d after randomization, intention-to-treat population (95% CI).
† Log-rank test.
‡ Median (interquartile range).
§ Inclusive of CMV syndrome, invasive disease, or CMV infection not meeting primary end point.
‖ Models from randomization to 300 d after randomization, intention-to-treat population.
¶ Adjusted for CMV-positive donor or -negative recipient.
** Adjusted for acute rejection before randomization.

Ann Int Med 2010; 152: 761

CMV

- Viremia
  - Viral load surveillance off prophylaxis
- Disease
  - Pneumonitis
  - GI
  - Occular
  - Bone Marrow
  - Other

- Treatment
  - Valgancyclovir
    - Risk of resistance
  - Gancyclovir (absorption)
  - Foscarnet
- Risk factor for rejection

Other Viral Infections

- Influenza
- Parainfluenza
- RSV
- Adenovirus
- Metapneumovirus

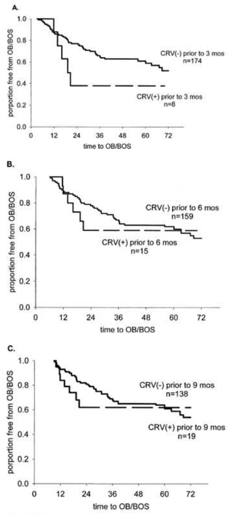
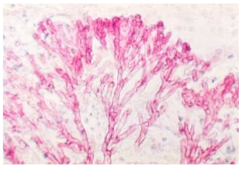
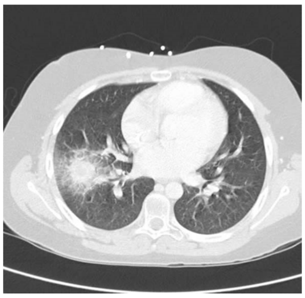


FIGURE 2 Landmark plots: proportion free from OB/BOS after CRV infection. Plots represent the proportion of patients free from OB/BOS after CRV infection at 3, 6, and 9 months after transplant compared with those patients who were not infected. CRV, community respiratory virus; OB/BOS, obliterative bronchiolitis/bronchiolitis obliterans syndrome.

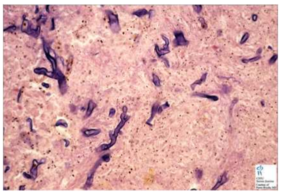
JHLT 2002; 26: 890



Aspergillus Infection



- Branching hyphae – acute angles
- Tracheobronchitis
  - Dehiscence
  - Airway obstruction
  - Stenosis
  - Malacia
- Parenchymal Disease
  - Ground glass
  - Alveolar infiltrate
  - “Halo sign”
  - Bronchiectasis
  - Hemoptysis
- Disseminated Disease

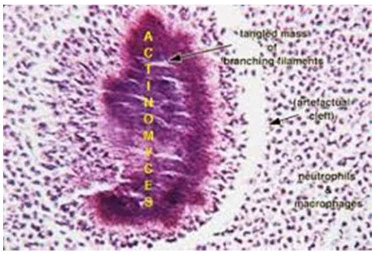


Rhizopus

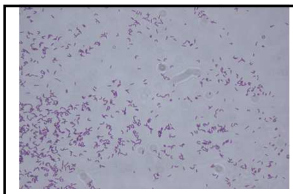
- Wide hyphae, few septations, right angles
- Infection:
  - Sinuses ⟶ CNS invasion
  - Pulmonary
  - Skin
  - Treatment:
    - Amphotericin
    - Surgical

Actinomycosis

- Anaerobic actinomycete
- Colonizes mouth and gums
- Mass like infiltrate
- Can invade bone, muscle and skin
- Characteristic sulfur granules
- Typically polymicrobial infection
- Treatment: PCN (doxy, sulfonamides)


ACTINOMYCES
tangled mass of branching filaments
(artefactual cleft)
neutrophils & macrophages

Rhodococcus



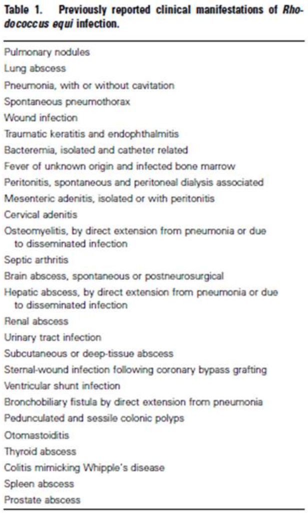


Table 1. Previously reported clinical manifestations of *Rhodococcus equi* infection.

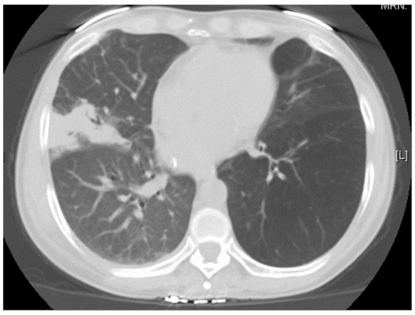
Pulmonary nodules
Lung abscess
Pneumonia, with or without cavitation
Spontaneous pneumothorax
Wound infection
Traumatic keratitis and endophthalmitis
Bacteremia, isolated and catheter related
Fever of unknown origin and infected bone marrow
Peritonitis, spontaneous and peritoneal dialysis associated
Mesenteric adenitis, isolated or with peritonitis
Cervical adenitis
Osteomyelitis, by direct extension from pneumonia or due to disseminated infection
Septic arthritis
Brain abscess, spontaneous or postneurosurgical
Hepatic abscess, by direct extension from pneumonia or due to disseminated infection
Renal abscess
Urinary tract infection
Subcutaneous or deep-tissue abscess
Sternal-wound infection following coronary bypass grafting
Ventricular shunt infection
Bronchobiliary fistula by direct extension from pneumonia
Pedunculated and sessile colonic polyps
Otomastoiditis
Thyroid abscess
Colitis mimicking Whipple's disease
Spleen abscess
Prostate abscess

- Aerobic actinomycete
- Can be confused with nocardia or corynebacterium
- Exposure to land and water animals
- Gram positive – can look like cocci or baccili
- Variable acid fast staining

Clin Inf Dis 2002; 34: 1379

Rhodococcus

- Treatment:
  - Susceptibility testing
  - Surgical debulking



Clin Inf Dis 2002; 34: 1379

PTLD: Presentation

- Earlier development – higher likelihood of disease limited to the thorax

- Unexplained fever (fever of unknown origin)
- Mononucleosis-like syndrome (fever, malaise, pharyngitis, tonsillitis)
- Gastrointestinal bleeding, obstruction, or perforation
- Abdominal-mass lesions
- Infiltrative disease of the allograft
- Hepatocellular or pancreatic dysfunction
- Central nervous system disease

- Treatment:
  - Limited: Rituxan
  - R-CHOP

Rejection - Mechanisms

- Primary Graft Dysfunction -> augmented allo-immunity, damage to epithelium/endothelium, airway fibrosis

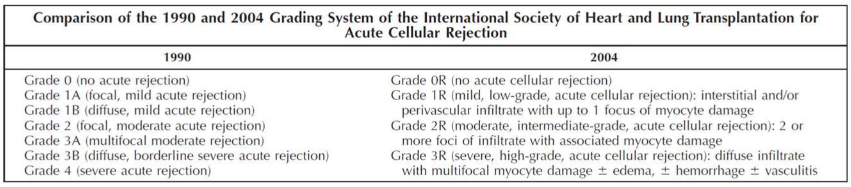
- Non-allo-immune insults (infection and non-infectious) activate innate immune response

- Auto-reactivity

- Absent or dysfunctional regulatory T cells impede tolerance

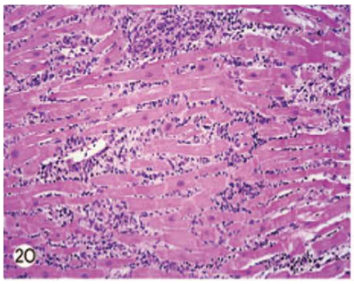
American Journal of Transplantation 2009; 9: 1714

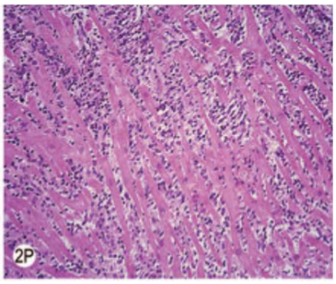
Acute Rejection



Comparison of the 1990 and 2004 Grading System of the International Society of Heart and Lung Transplantation for Acute Cellular Rejection

1990	2004
Grade 0 (no acute rejection) Grade 1A (focal, mild acute rejection) Grade 1B (diffuse, mild acute rejection) Grade 2 (focal, moderate acute rejection) Grade 3A (multifocal moderate rejection) Grade 3B (diffuse, borderline severe acute rejection) Grade 4 (severe acute rejection)	Grade 0R (no acute cellular rejection) Grade 1R (mild, low-grade, acute cellular rejection): interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage Grade 2R (moderate, intermediate-grade, acute cellular rejection): 2 or more foci of infiltrate with associated myocyte damage Grade 3R (severe, high-grade, acute cellular rejection): diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis





Arch Pathol Lab Med 2007; 131: 1169

Treatment of Acute Rejection

- Augmented immune suppression
- Evaluation for inciting factors:
  - GERD
  - Recurrent Infection (CMV)
  - Reservoirs of infection
- Close monitoring of spirometry, pathology

Risk Factors

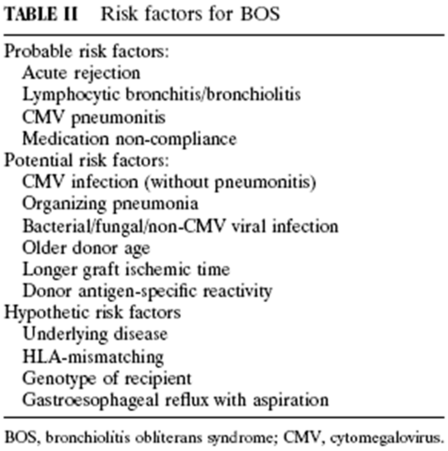


TABLE II Risk factors for BOS

Probable risk factors:
Acute rejection
Lymphocytic bronchitis/bronchiolitis
CMV pneumonitis
Medication non-compliance
Potential risk factors:
CMV infection (without pneumonitis)
Organizing pneumonia
Bacterial/fungal/non-CMV viral infection
Older donor age
Longer graft ischemic time
Donor antigen-specific reactivity
Hypothetic risk factors
Underlying disease
HLA-mismatching
Genotype of recipient
Gastroesophageal reflux with aspiration

BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus.

J Heart Lung Transplant 2002; 21: 297

Chronic Rejection - Management

- Modifiable risk factors:
  - Noncompliance/subtherapeutic immune suppression
  - GERD
  - Antibody mediated rejection
- Augmented immune suppression:
  - Within class
  - Additional
- Anti-inflammatory
  - Azithromycin
  - Statins
- ECP
- Anti-Lymphocyte Therapy
- Repeat Transplantation

Manifestations of Antibody Mediated Allograft Injury

- Hyperacute Rejection:
  - Best described
  - Neutrophilic infiltrates, endothelial and epithelial damage, IgG staining
  - Can be fatal
  - Less common with cross-matching procedures

JHLT 2010; 29: 395

National Conference to Assess AMR in Solid Organ Transplant

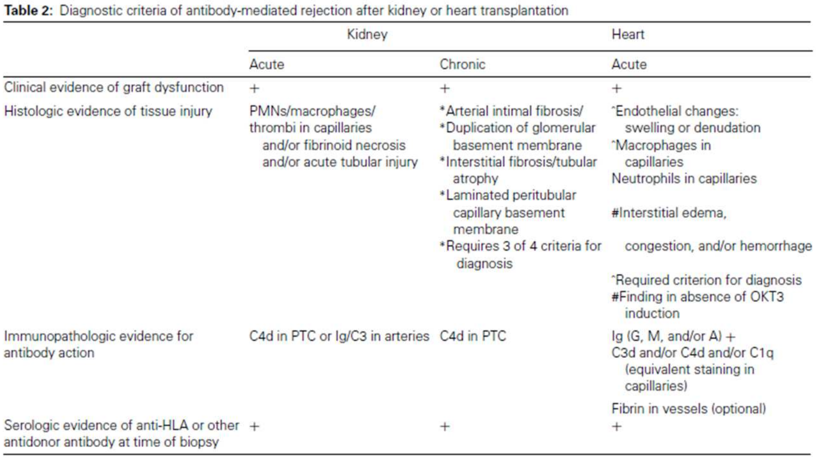


Table 2: Diagnostic criteria of antibody-mediated rejection after kidney or heart transplantation

	Kidney		Heart
	Acute	Chronic	Acute
Clinical evidence of graft dysfunction	+	+	+
Histologic evidence of tissue injury	PMNs/macrophages/ thrombi in capillaries and/or fibrinoid necrosis and/or acute tubular injury	*Arterial intimal fibrosis/ *Duplication of glomerular basement membrane *Interstitial fibrosis/tubular atrophy *Laminated peritubular capillary basement membrane *Requires 3 of 4 criteria for diagnosis	^Endothelial changes: swelling or denudation ^Macrophages in capillaries Neutrophils in capillaries #Interstitial edema, congestion, and/or hemorrhage ^Required criterion for diagnosis #Finding in absence of OKT3 induction
Immunopathologic evidence for antibody action	C4d in PTC or Ig/C3 in arteries	C4d in PTC	Ig (G, M, and/or A) + C3d and/or C4d and/or C1q (equivalent staining in capillaries) Fibrin in vessels (optional)
Serologic evidence of anti-HLA or other antidonor antibody at time of biopsy	+	+	+

Am J Transplant 2004; 4: 1033

Non-Allograft Associated Complications

- HTN
- Hyperlipidemia
- Renal Dysfunction
- DM
- Osteoporosis
- Malignancy
  - Skin
  - PTLD
  - Other

Toxicities of Immune Suppression

- Induction:
  - Cytopenias

- Calcineurin Inhibitors (Prograf/Cyclosporine):
  - Nephrotoxicity – afferent arteriolar vasoconstriction
  - CNS: PRES
  - Heme: HUS/TMA
  - Electrolyte abnormalities – hyperkalemia, hypomagnesemia, hypophosphatemia

- Purine Modulators (Mycophenolate/Azathioprine):
  - Cytopenias
  - Liver toxicity
  - GI toxicity

Toxicities of Prophylaxis

- Valgancyclovir:
  - Cytopenias
- Bactrim:
  - Hyperkalemia
  - Nephrotoxicity
  - Leukopenia

Summary

- Substantial overlap between general ICU care and care of the transplant recipient
- Care of the transplant recipient requires a multidisciplinary, collaborative approach
- Special considerations:
  - Technical concerns
  - Primary graft dysfunction
  - Immunologic issues
  - Infectious issues
  - Medication side effects

Transplant Teams:
Continuing a Tradition
of Excellence

DONATE
LIFE

Disclosures

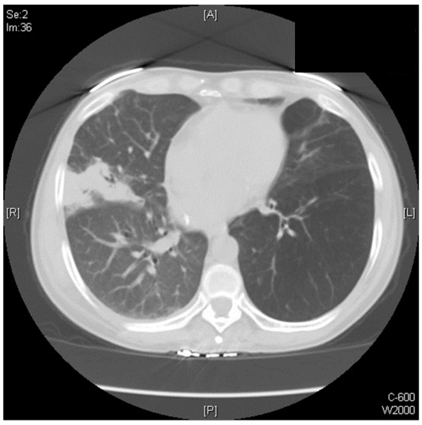
- Some references to off label use of medications
- Site PI – pharmaceutical trials:
  - Gilead
  - Genentech

Case Discussion

- A 56-year-old woman presents one year after right single lung transplantation for COPD. Her post-transplant course has been complicated by persistent neutropenia. She has been maintained on tacrolimus and prednisone, but because of her neutropenia, has required intermittent cessation of mycophenolate mofetil. She has also received only intermittent cytomegaolvirus prophylaxis due to her neutropenia.
- The patient presents with a one-month history of increasing dyspnea and cough. She reports significant weight loss and poor appetite during this period. She denies fever, chills, or sweats. Review of systems is otherwise negative. The patient denies travel or sick contacts. She recently visited the state fair, but otherwise denies unusual exposures.

Question 1

- On exam, the patient is afebrile with a respiratory rate of 20 breaths per minute and oxygen saturation of 96% on room air. Exam is notable for markedly diminished breath sounds in the native lung, but the allograft is clear to auscultation. A chest CT scan demonstrates a new infiltrate in the allograft.
-



Question 1

- A bronchoscopy with broncho-alveolar lavage is performed and results are pending. The patient reports improvement in her shortness of breath after empiric treatment with a fluoroquinolone. Two of four blood cultures subsequently return positive for corynebacterium diphteroids, with “medium” suspicion for true pathogenicity based on growth pattern.
- The most likely cause of the patient’s pneumonia is:
  a) Corynebacterium diphteroids
  b) Cytomegalovirus
  c) Nocardia
  d) Rhodococcus
  e) Acute allograft rejection

Question 1

- A bronchoscopy with broncho-alveolar lavage is performed and results are pending. The patient reports improvement in her shortness of breath after empiric treatment with a fluoroquinolone. Two of four blood cultures subsequently return positive for corynebacterium dyptheroids, with "medium" suspicion for true pathogenicity based on growth pattern.

- The most likely cause of the patient's pneumonia is:
  a) Corynebacterium dyptheroids
  b) Cytomegalovirus
  c) Nocardia
  d) Rhodococcus
  e) Acute allograft rejection

Question 2

- All of the following are potential causes of thrombocytopenia/coagulopathy after thoracic organ transplantation except:

  a) 1) Bridge to transplant with mechanical circulatory support
  b) 2) Induction immune suppression with anti-thymocyte globulin
  c) 3) Pre-emptive fungal prophylaxis with micafungin
  d) 4) IV Metoprolol for management of atrial fibrillation
  e) 5) Intra-operative cardiopulmonary bypass

Question 2

- All of the following are potential causes of thrombocytopenia/coagulopathy after thoracic organ transplantation except:

a) Bridge to transplant with mechanical circulatory support
b) Induction immune suppression with anti-thymocyte globulin
c) Pre-emptive fungal prophylaxis with micafungin
d) IV Metoprolol for management of atrial fibrillation
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Mechanical Support Devices in the ICU: Temporary Mechanical Circulatory Support (MCS)

Phillip C. Camp, Jr., MD
Harvard Faculty

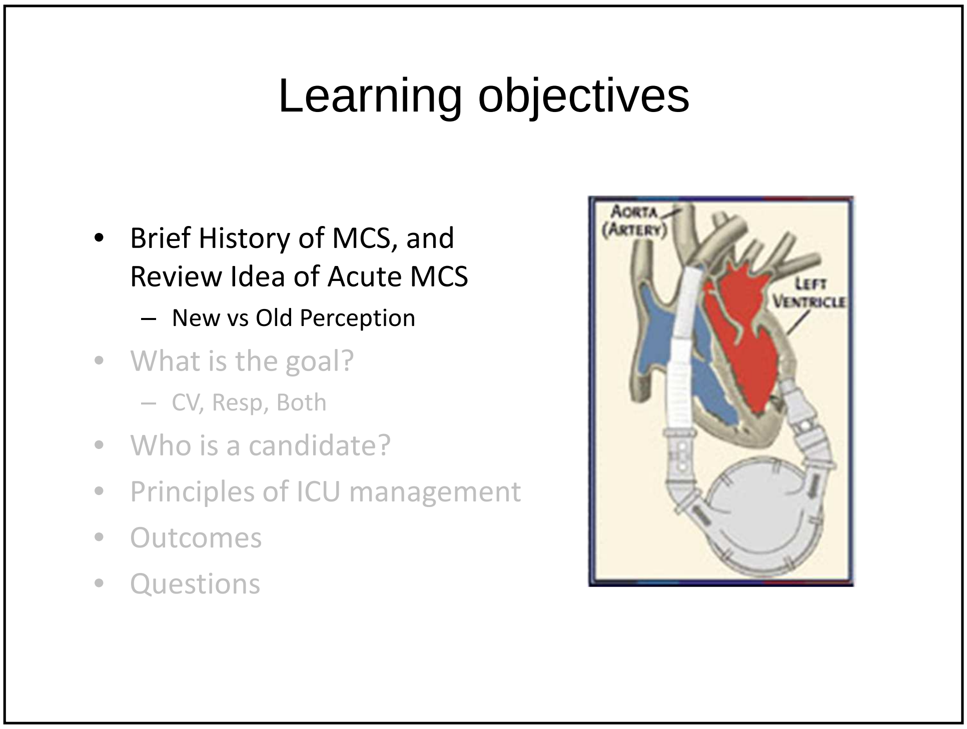
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Conflict of interest disclosures

- None

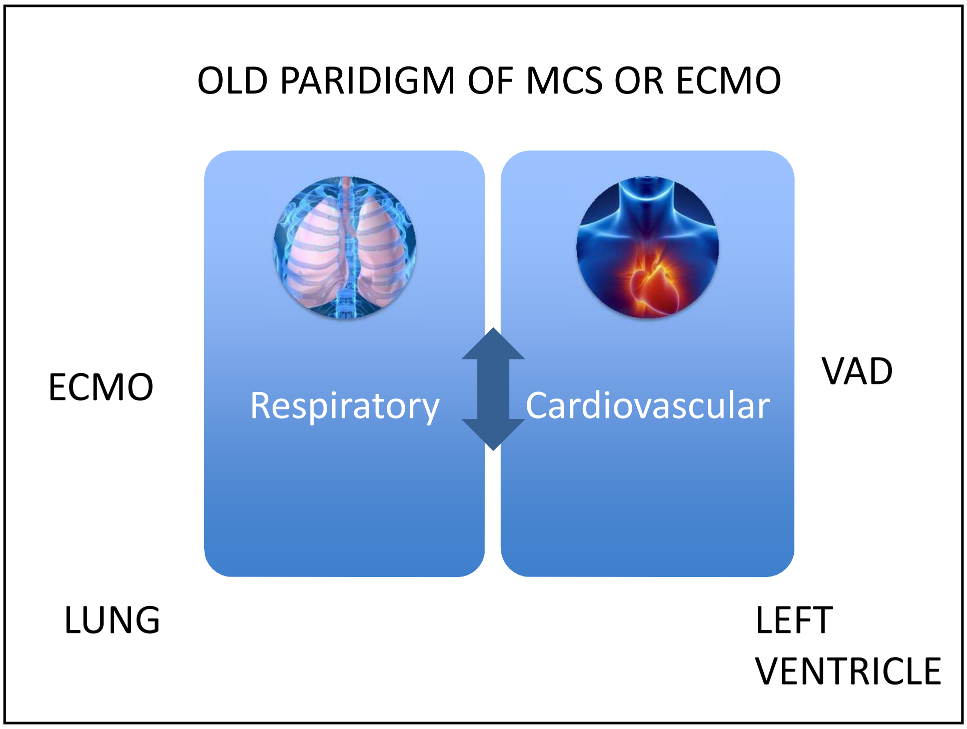
- Specific Products or devices will be named in this lecture but I have NO relationship with any company NOR should using a specific product be considered an endorsement of a specific product or technique



Learning objectives

- Brief History of MCS, and Review Idea of Acute MCS
  - New vs Old Perception
- What is the goal?
  - CV, Resp, Both
- Who is a candidate?
- Principles of ICU management
- Outcomes
- Questions

Aorta (Artery)
Left Ventricle



OLD PARIDIGM OF MCS OR ECMO

ECMO

Respiratory

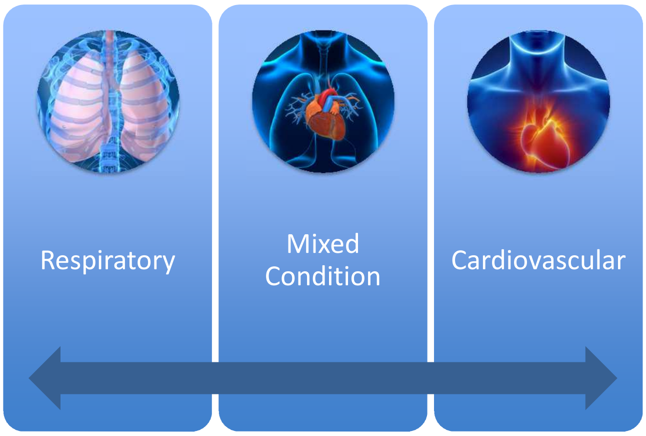
Cardiovascular

VAD

LUNG

LEFT VENTRICLE

NEW PARIDIGM OF MCS AND ECLS



Respiratory

Mixed Condition

Cardiovascular

LUNG

RIGHT VENTRICLE

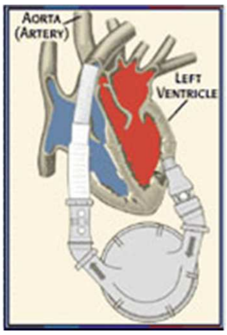
BOTH VENTRICLES

LEFT VENTRICLE

Learning objectives

"Mechanical Support"

- Brief History of MCS
- Review of Acute MCS
  - New vs Old Perception
- What is the goal?
  - CV, Resp, Both
- Who is a candidate?
- Principles of ICU management
- Outcomes
- Questions



MECHANICAL CIRCULATORY AND PULMONORESPIRATORY SUPPORT

- Primary Driver of Need and Innovation has been Heart Failure
  - 825,000 new cases each year
  - Significant incidence of acute cardiovascular collapse and respiratory failure
- Innovative interventions and therapies have created increased need for temporary but advanced mechanical support to allow time for Diagnostics / Intervention / Therapy

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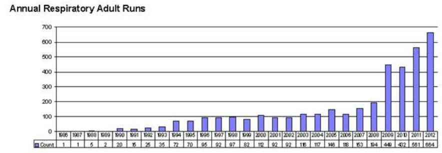
Historical perspective on mechanical circulatory support.



1960

1963: First report of implantable artificial ventricle by Liotta
1964: NIH forms Artificial Heart Program
1966: First successful pneumatic LVAD implanted by Debakey for post-cardiotomy wean and bridge to recovery
1969: Denton Cooley uses first TAH as bridge to transplant for postcardiotomy shock

1970

1970: NIH forms working group to explore VADs
1977: NIH request for proposals for components of long-term implantable pumps
1978: Norman et al. report first use of LVAD as bridge to transplant for postcardiotomy stone heart syndrome

1980

1980: NIH second request for proposals for long-term implantable LVAD
1982: Implant of first total artificial heart (Jarvik-7) intended for permanent support
1984: First successful implant of electrically-driven Novacor LVAD as bridge to transplant for chronic heart failure.
1984: CMS defines strategies for LVAD support

1990

1992: FDA approves Abiomed 5000 as bridge to transplant
1994: FDA approves pneumatic LVAD (Thermo Cardiosystems) as bridge to transplant
1995: FDA approves electrical LVAD (Thoratec XVE) as bridge to transplant
1998: FDA approves Novacor and Thermo Cardiosystems LVADs as bridge to transplant

2000

2001: REMATCH shows HeartMate XVE superior to optimal medical therapy for transplant-ineligible patients with advanced heart failure
2003: Landmark FDA approval of Thoratec HeartMate XVE for destination therapy
2004: Reports of SynCardia total artificial heart success as in-hospital bridge to transplant for biventricular failure leads to FDA approval
2006: Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) established
2007: First report of continuous flow LVAD (Thoratec HeartMate II) as bridge to transplant
2008: FDA approves continuous flow LVAD (HeartMate II) for bridge to transplant
2009: Thoratec HeartMate II superior to HeartMate XVE as destination therapy

2010

2010: FDA approves Thoratec HeartMate II for destination therapy
2010: Preliminary results of HeartWare intra-pericardial continuous flow VAD as bridge to transplant (ADVANCE study)
2011: NHLBI-sponsored REVIVE-IT study to compare LVAD with medical therapy in stable NYHA III patients

Garrick C. Stewart, and Michael M. Givertz Circulation. 2012;125:1304-1315

American Heart Association.

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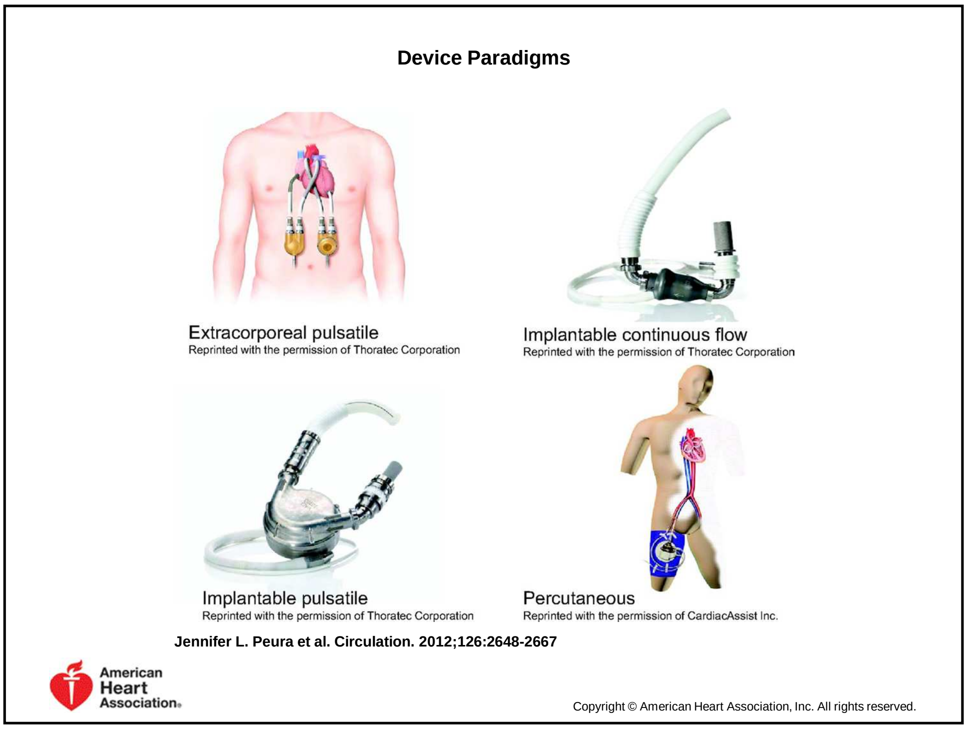

Device Paradigms

Extracorporeal pulsatile
Reprinted with the permission of Thoratec Corporation

Implantable continuous flow
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Implantable pulsatile
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Percutaneous
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Jennifer L. Peura et al. Circulation. 2012;126:2648-2667

American Heart Association

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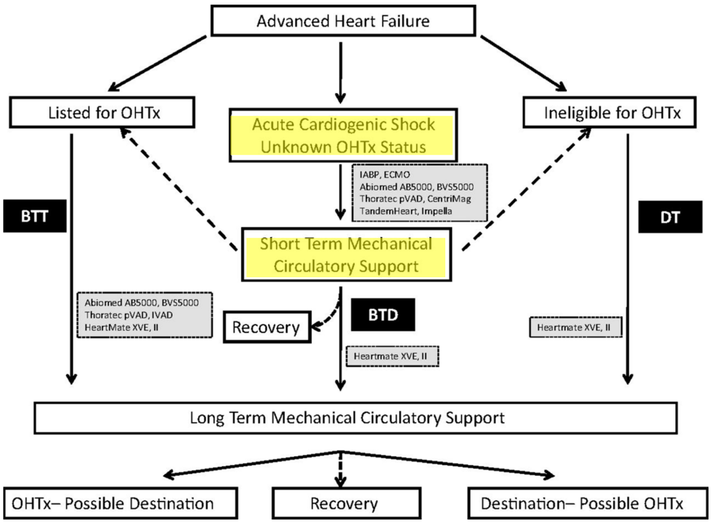
MECHANICAL CIRCULATORY AND PULMONORESPIRATORY SUPPORT

- Improved Engineering
  - Durability, Capacity, Size, Innovation
- Significant Technologic Development or Improvements
  - IABP
  - ECMO (ECLS)
    - Device, Oxgenators, Cannula
  - Percutanous VAD’s (Tandem Heart, Impella)
    - Size, Flow Rates
  - Extracorporeal “Short Term” VAD’s
- Revolution from Durable Mechanical Support, to Acute and Short-term Mechanical support develops
- Evolution to a “Spectrum of Mechanical Support”
  - ECMO becomes ECLS…. Or even a variant of MCS

Device selection flow chart: Example for Cardiac +/- Pulmonary Failure



Advanced Heart Failure

Listed for OHTx

Acute Cardiogenic Shock
Unknown OHTx Status

Ineligible for OHTx

IABP, ECMO
Abiomed AB5000, BVS5000
Thoratec pVAD, CentriMag
TandemHeart, Impella

BTT

DT

Short Term Mechanical
Circulatory Support

Abiomed AB5000, BVS5000
Thoratec pVAD, IVAD
HeartMate XVE, II

Recovery

BTD

Heartmate XVE, II

Heartmate XVE, II

Long Term Mechanical Circulatory Support

OHTx– Possible Destination

Recovery

Destination– Possible OHTx

Jennifer L. Peura et al. Circulation. 2012;126:2648-2667

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Goals of Temporary MCS

- Augment or Replace Cardiac Output
  - Decrease Preload
  - Decrease Afterload
  - Provide Myocardial Rest
    - Right and Left
- Augment or Replace Gas Exchange
  - Improve Oxygenation
  - Improve CO2 Clearance and pH maintenance
  - Provide Pulmonovascular Rest
- Preserve Adequate Organ Perfusion and Oxygen Delivery

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Goals of Temporary MCS:
Arenas of Support

- Acute Injury
  - ACS
  - Acute Myocarditis
  - Cardiac Arrest of Unknown Etiology
  - Pulmonary Embolus
  - Amniotic Embolus
  - Trauma
  - Aspiration
  - Isolated Respiratory Failure
    - Infection
    - Reactive Airway Disease
  - Poisoning

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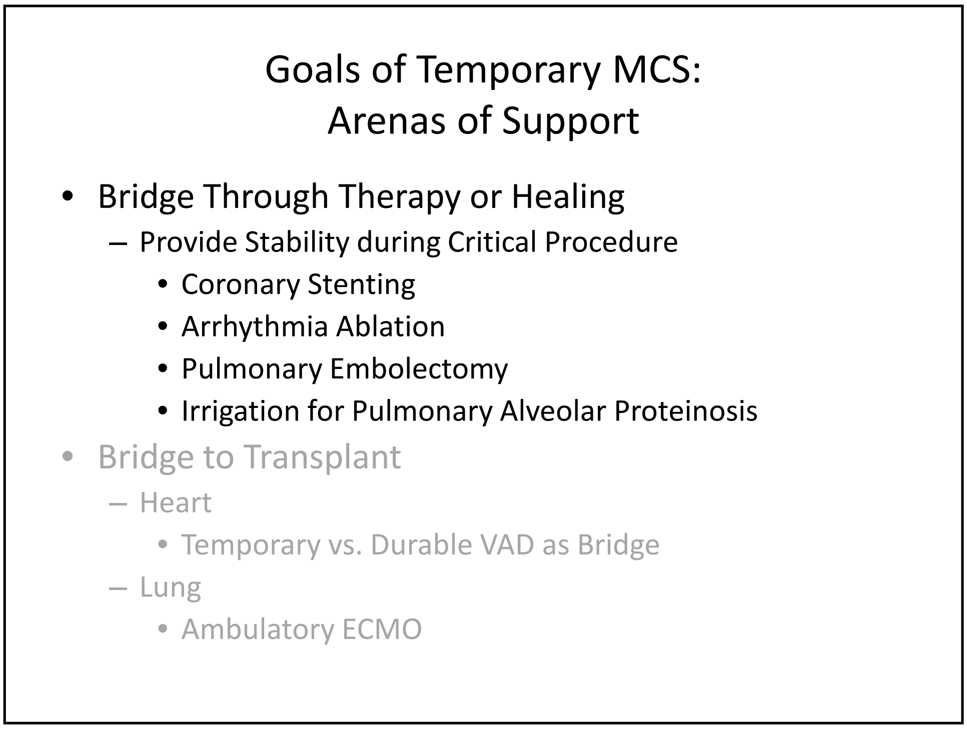
  - Trauma
  - Aspiration
  - Isolated Respiratory Failure
    - Infection
    - Reactive Airway Disease
  - Poisoning

Goals of Temporary MCS: Arenas of Support

- Induced Injury
  - Post Cardiotomy CV Shock / Failure
  - TRALI

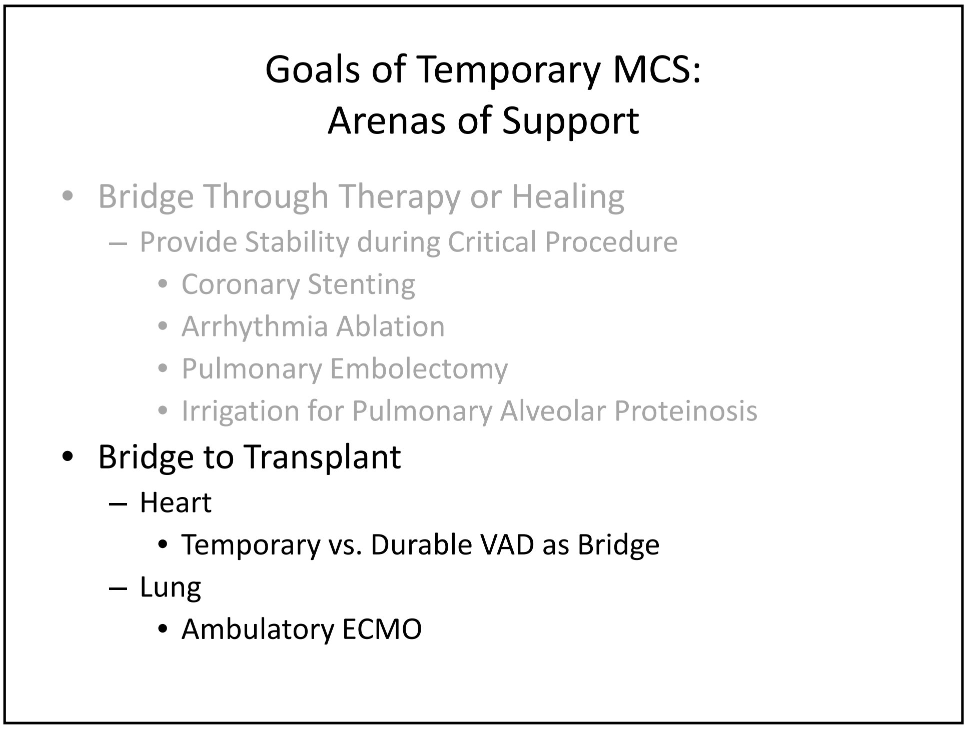
  - Post Transplant (Heart, Lung) Organ Dysfunction
    - 15% expected “significant” Dysfunction following implant (Ischemia-Reperfusion Injury)
    - Early RV dysfunction after Implant
    - LV Failure in setting of prolonged pHTN

  - S/P Pulmonary Surgery Respiratory Failure



Goals of Temporary MCS: Arenas of Support

- Bridge Through Therapy or Healing
  - Provide Stability during Critical Procedure
    - Coronary Stenting
    - Arrhythmia Ablation
    - Pulmonary Embolectomy
    - Irrigation for Pulmonary Alveolar Proteinosis
- Bridge to Transplant
  - Heart
    - Temporary vs. Durable VAD as Bridge
  - Lung
    - Ambulatory ECMO



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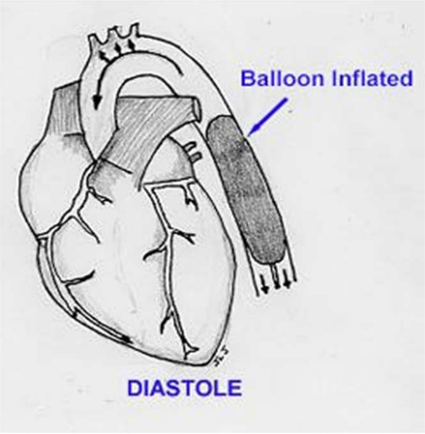
  - Lung
    - Ambulatory ECMO

Intra-Aortic Balloon Pump (IABP)

Intra-Aortic Balloon Pump (IABP)

- Kantrowitz demonstrated survival in cardiac shock in 1968
- Scheidt then showed improved hemodynamics, increased cardiac output and decreased lactic acidosis
- Proven reliability and performance
- Decreases LV preload, LV end-diastolic pressure, LV wall stress and afterload.
- Decreases Myocardial Oxygen Demand
- Improves Coronary Blood Flow, Systemic Blood Pressure
- Decreases oxygen consumption

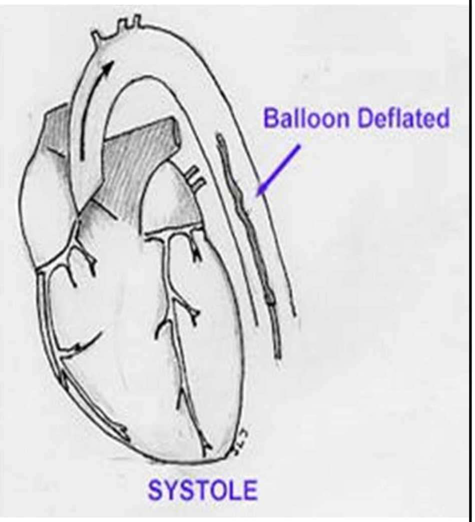
- No side effects of systemic medications



- The balloon is inflated during diastole in sync with the closure of the aortic valve.

- The blood in the aortic arch above the level of the balloon is pushed backward providing increased coronary artery blood flow and increased myocardial oxygen supply.

- The balloon is deflated just before systole which helps to decrease afterload.
- The space where the balloon was inflated creates an empty space where the blood doesn't have to flow against any resistance.

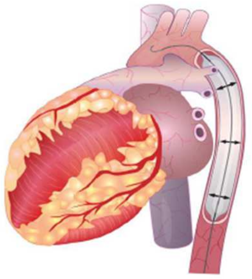


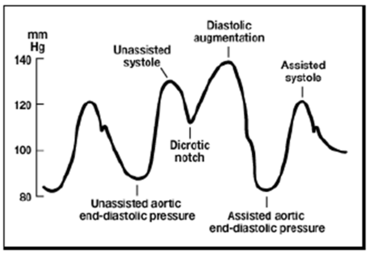
IAPB: Indications

- Cardiogenic shock after acute infarction
- Left ventricular failure in the postoperative cardiac surgery patient
- Severe unstable angina
- Postinfarction ventricular septal defect or mitral regurgitation
- Short-term bridge to Cardiac Transplantation
- Support during High Risk Procedure

Temporary MCSD: IABP

- Most common form of MSC
- Greatest benefit in those with myocardial ischemia





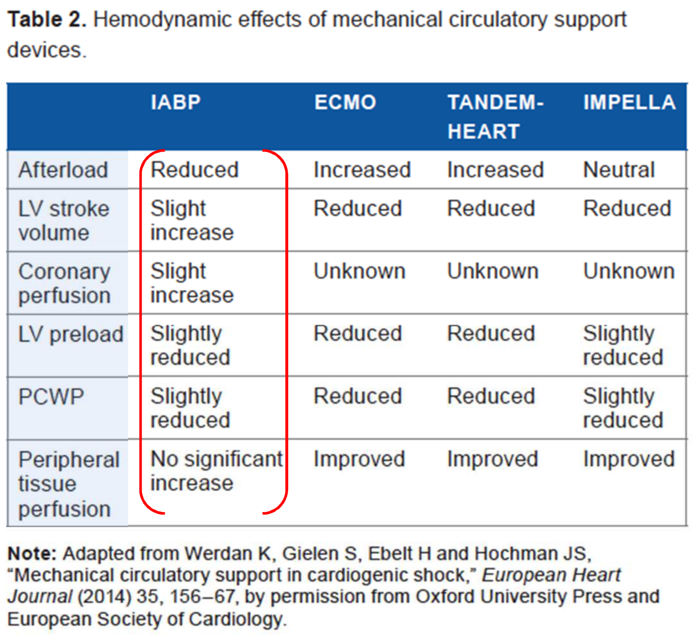


Table 2. Hemodynamic effects of mechanical circulatory support devices.

	IABP	ECMO	TANDEM-HEART	IMPELLA
Afterload	Reduced	Increased	Increased	Neutral
LV stroke volume	Slight increase	Reduced	Reduced	Reduced
Coronary perfusion	Slight increase	Unknown	Unknown	Unknown
LV preload	Slightly reduced	Reduced	Reduced	Slightly reduced
PCWP	Slightly reduced	Reduced	Reduced	Slightly reduced
Peripheral tissue perfusion	No significant increase	Improved	Improved	Improved

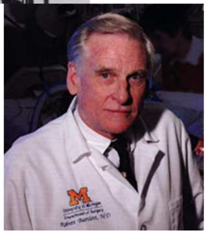
Note: Adapted from Werdan K, Gielen S, Ebelt H and Hochman JS, "Mechanical circulatory support in cardiogenic shock," *European Heart Journal* (2014) 35, 156–67, by permission from Oxford University Press and European Society of Cardiology.

Extracorporeal Membrane Oxygenation (ECMO)
[Extracorporeal Life Support]

A history of ECMO

- 1937 the first heart-lung machine was built by John Heysham Gibbon (performed the first human open heart surgery), considered the inventor of the heart-lung or pump oxygenator.
- 1953 the first heart lung bypass machine was first used on a human
- 1960, it was considered safe to use the CBM along with hypothermia to perform CABG surgery.
- 1963 –silicone membrane gas exchange device
- 1974 – Drinker (inventor of the iron lung) et al BWH participated in a 9 center study
- 1976 – Bartlett, 1st Neonatal survivor of ECMO after Meconium Aspiration Syndrome

Gibbon and his first patient from 1953 (photo taken 1963)



Bartlett was a Surgical Intern, Resident, and Senior Resident at BWH and CH. In 1968, he was the Chief Resident in Thoracic Surgery and the following year served as its Chief Resident Surgeon. While at Brigham, he was a Research Fellow in Surgery, named the Arthur Tracy Cabot Teaching Fellow in Surgery, and became a Harvey Cushing Fellow. He also was a National Institutes of Health Trainee in Academic Surgery at Harvard Medical School.

First Adult Landmark Study

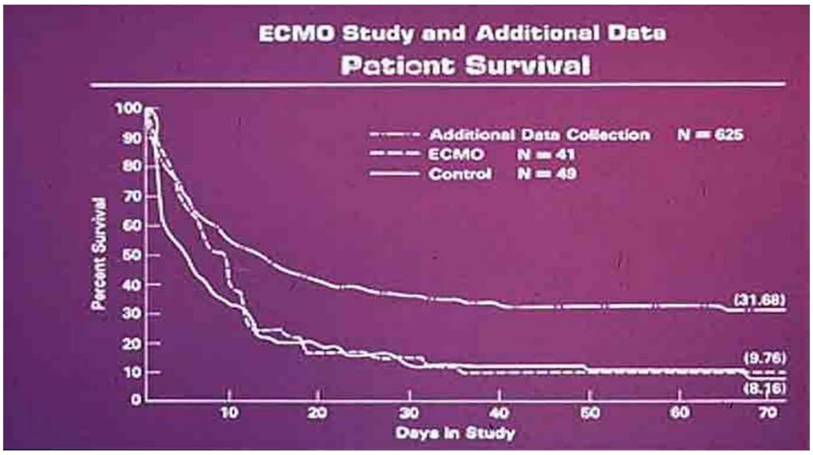
Extracorporeal Membrane Oxygenation in Severe Acute Respiratory Failure: A Randomized Prospective Study

Zapol WM, et al. JAMA 242: 1979.

NIH Study on Adults with ARDS

- 90 patients enrolled
- Conventional Therapy = 8.3% survival
- ECMO = 9.5% survival
- Enrollment terminated early due to lack of increased survival
- Wide variation in patients, centers, care

Randomized trial ECMO vs conventional ventilation for ARDS



- Effectively ended the use of ECMO in Adults for years

JAMA. 1979 Nov 16;242(20):2193-6.

What did ECMO look like?

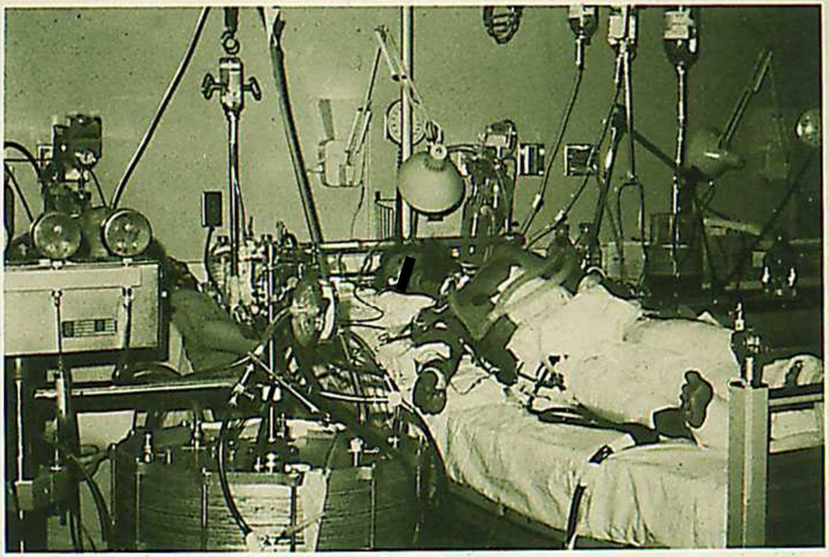
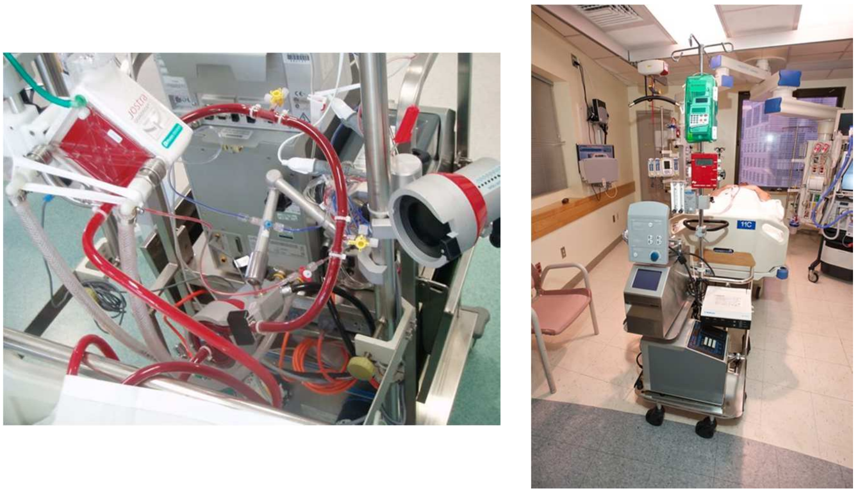
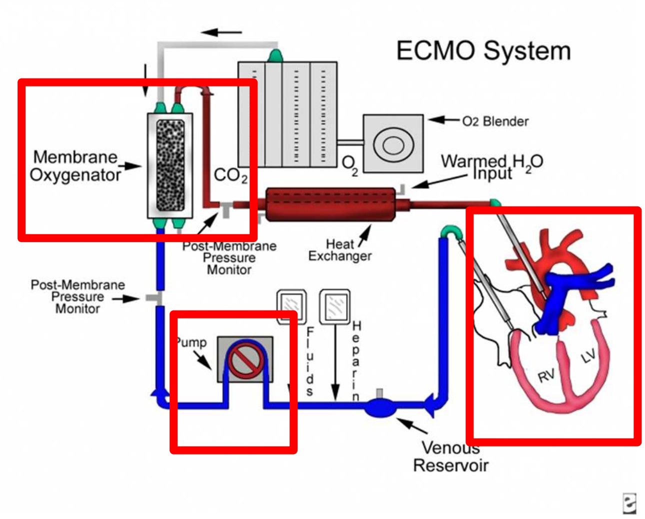


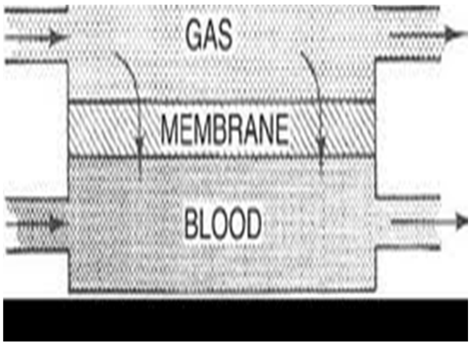
FIGURE 3.4 The first successful extracorporeal life support patient, treated by J. Donald Hill using the Bramson oxygenator (foreground), Santa Barbara, 1971.

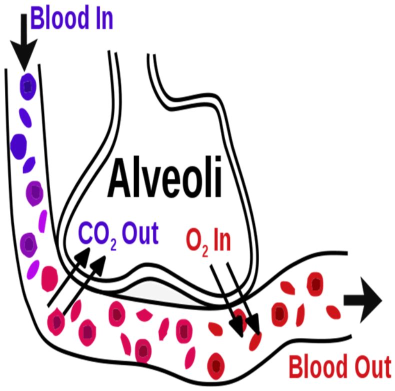
What does it look like today…



ECMO Basics


ECMO System
Membrane Oxygenator
CO$_2$
O2 Blender
O$_2$
Warmed H$_2$O Input
Post-Membrane Pressure Monitor
Heat Exchanger
Post-Membrane Pressure Monitor
Pump
Fluids
Heparin
Venous Reservoir
RV
LV


GAS
MEMBRANE
BLOOD


Blood In
Alveoli
CO_2 Out
O_2 In
Blood Out

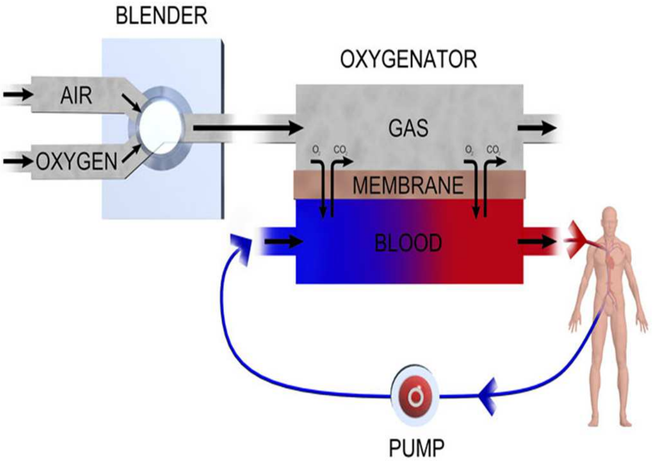
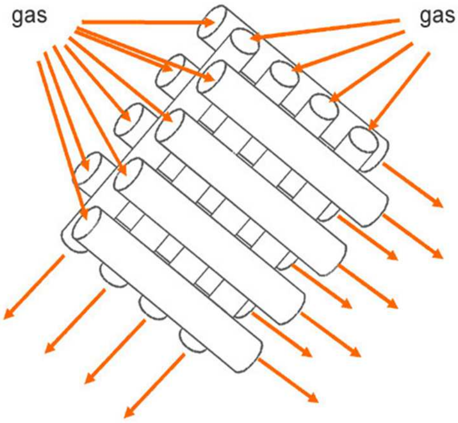


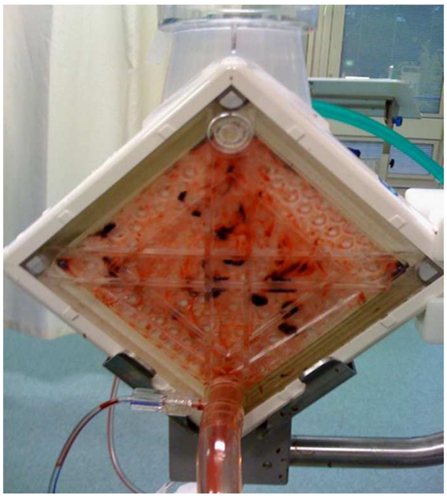
Illustration: Lara Durrant and Peter Kuempel

BLENDER
AIR
OXYGEN
OXYGENATOR
GAS
O_2
CO_2
O_2
CO_2
MEMBRANE
BLOOD
PUMP

How ECMO Works:

The oxygenator in venovenous ECMO. The ECMO pump delivers venous blood to the oxygenator. This device is divided into two separate chambers by a semipermeable membrane. The venous blood enters the oxygenator and travels along one side of the membrane (the blood side), while fresh gas, known as sweep gas, is delivered to the other side (the gas side). Gas exchange (oxygen uptake and CO_2 elimination) take place across the membrane. The oxygenated blood is then reinfused into the patient's venous system. The composition of the gas on the gas side of the oxygenator membrane is determined by adjustment of a blender that mixes room air with oxygen for delivery into the oxygenator.

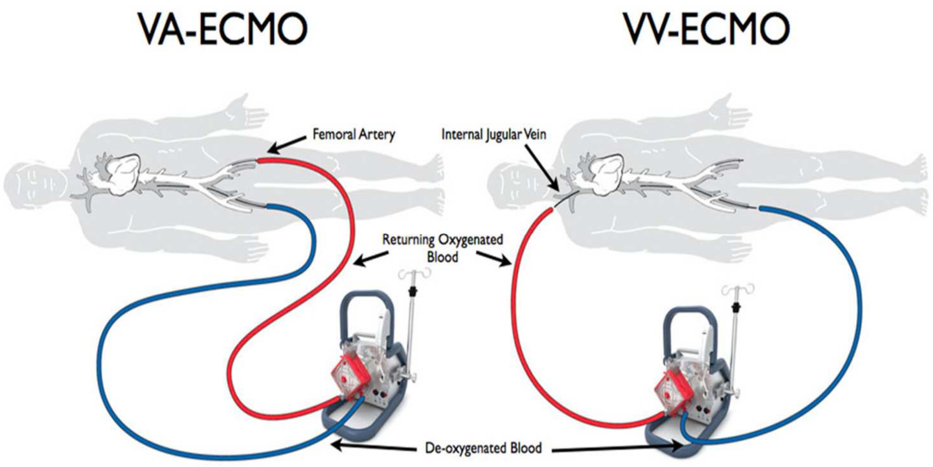

gas
gas

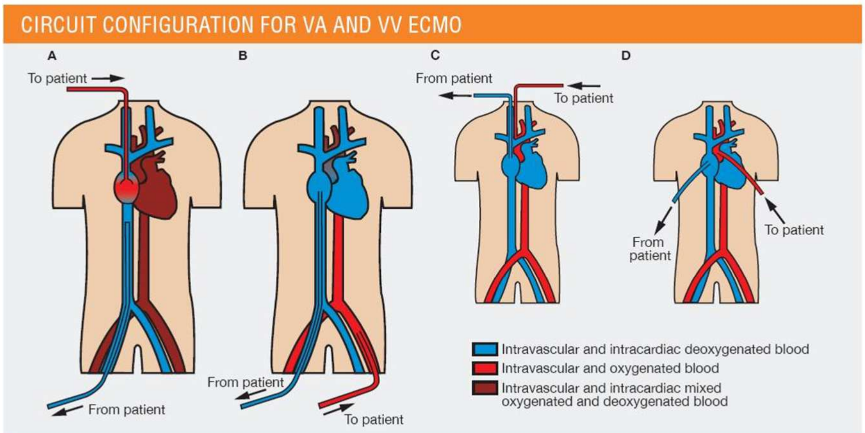


Extracorporeal Membrane Oxygenation (ECMO) [Extracorporeal Life Support]

- Ability to be pure Respiratory support, or combined cardiovascular and respiratory support
- Can be centrally or peripherally interfaced with patient
- Can be done ANYWHERE in a healthcare facility
- Various techniques for gaining vascular access
- Various modes of support can be provided
- Can allow for mobilization of patients while on full temporary support

ECMO Support

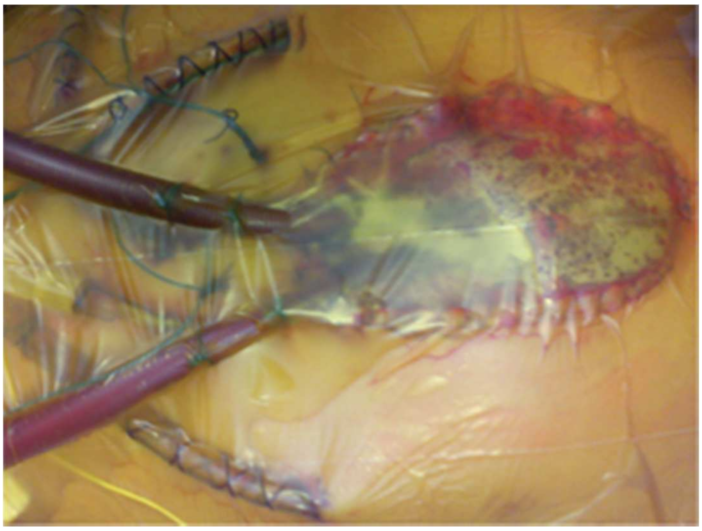

VA-ECMO
VV-ECMO
Femoral Artery
Internal Jugular Vein
Returning Oxygenated Blood
De-oxygenated Blood

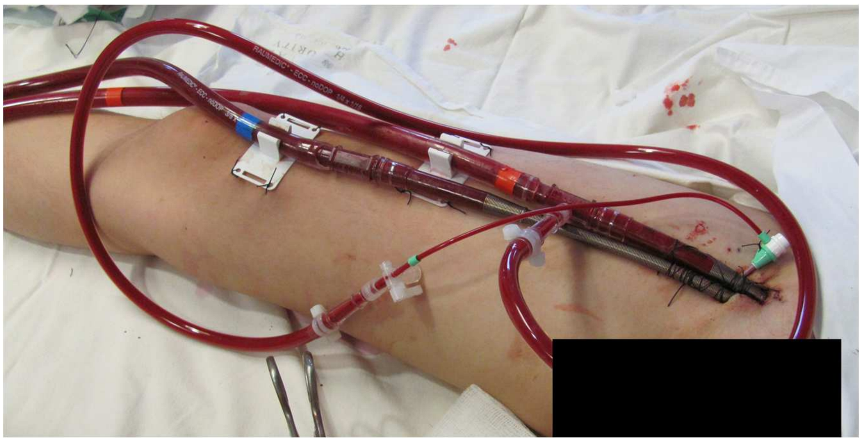

CIRCUIT CONFIGURATION FOR VA AND VV ECMO

A
B
C
D
To patient
From patient
From patient
To patient
From patient
To patient
From patient
To patient
From patient
Intravascular and intracardiac deoxygenated blood
Intravascular and oxygenated blood
Intravascular and intracardiac mixed oxygenated and deoxygenated blood

A, VV ECMO; B, VA ECMO, femoral cannulation; C, VA ECMO, carotid cannulation; *D*, VA ECMO, thoracic cannulation. Reproduced from: Gaffney AM, Wildhirt SM, Griffin MJ, Annich GM, Randomski MW. Extracorporeal life support. BMJ. 2010;341:982-986. Copyright © 2010, *British Medical Journal*; with permission from BMJ publishing group.

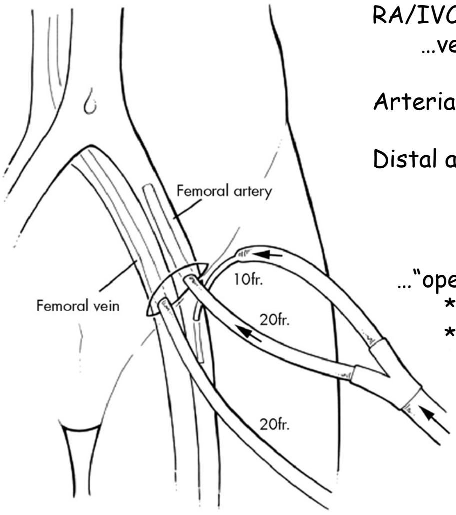
Figure 1.





[redacted]

Femoral cannulation for veno-arterial (VA) ECMO …


Femoral artery
10fr.
Femoral vein
20fr.
20fr.

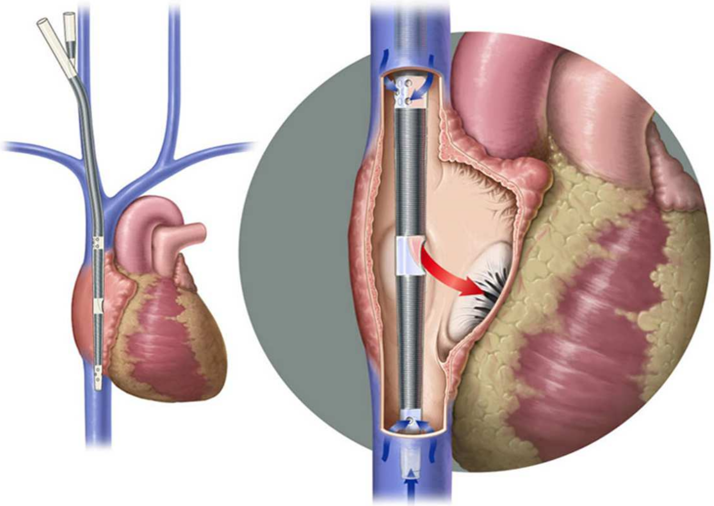
RA/IVC drainage from CFV access (23/25F)
…venous return limits flow

Arterial inflow (17F) … "downsize"

Distal arterial inflow (6F) … "downsize"

…"open" versus "percutaneous" access ?
*no complications
*exit strategy

Ideal VV ECMO cannula



BRIGHAM AND
WOMEN'S HOSPITAL

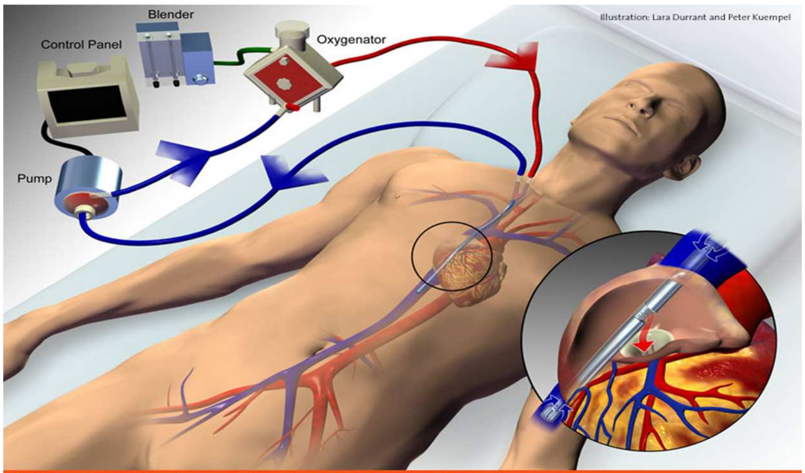
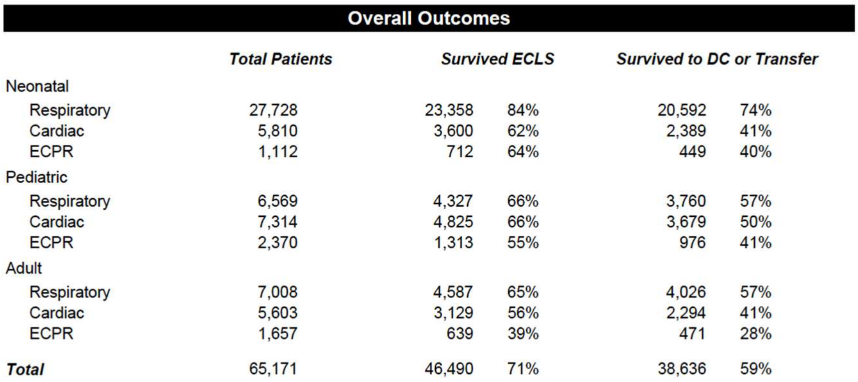


Illustration: Lara Durrant and Peter Kuempel

Single-site approach to venovenous ECMO cannulation:
A dual-lumen cannula is inserted in the internal jugular vein (extending through the right atrium and into the inferior vena cava). Venous blood is withdrawn through one "drainage" lumen with ports in both the superior and inferior vena cava. Reinfusion of oxygenated blood occurs through the second lumen, with a port situated in the right atrium. Inset: The two ports of the "drainage" lumen are situated in the superior and inferior vena cavae, distant from the reinfusion port. The reinfusion port is positioned so that oxygenated blood is directed across the tricuspid valve and directly into the right ventricle. This arrangement significantly reduces recirculation of blood when the cannula is properly positioned.

ECMO Outcomes



Overall Outcomes

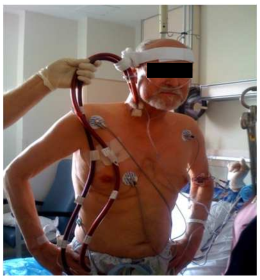
	Total Patients	*Survived ECLS*		*Survived to DC or Transfer*	
Neonatal					
Respiratory	27,728	23,358	84%	20,592	74%
Cardiac	5,810	3,600	62%	2,389	41%
ECPR	1,112	712	64%	449	40%
Pediatric					
Respiratory	6,569	4,327	66%	3,760	57%
Cardiac	7,314	4,825	66%	3,679	50%
ECPR	2,370	1,313	55%	976	41%
Adult					
Respiratory	7,008	4,587	65%	4,026	57%
Cardiac	5,603	3,129	56%	2,294	41%
ECPR	1,657	639	39%	471	28%
Total	65,171	46,490	71%	38,636	59%

ELSO Jan 2015 Data Summ

Ambulatory ECMO

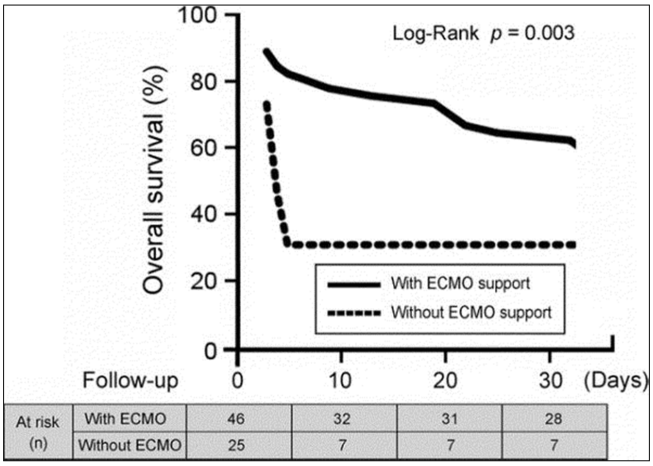
Bridge to Lung Transplantation

	1970s	1980s	1990–2000	2000–2010	2010–June 2011
Patients listed for lung transplantation on ECMO	1	1	22	104	56
Modes of ECLS used	VA	VA	VA	VV, VA, iLA™	VV, VA, iLA™, hybrid
Pump configuration	CPB	Roller-pump	Roller-pump	Centrifugal	Centrifugal
Oxygenator membrane	Silicone membrane	Polypropylene and silicone	Polypropylene	PMP	PMP
Cannulation approach innovation	Central	Central	Central	Peripheral Novalung®	Peripheral Avalon™



ASAIO Journal 2013;59:3-10

High Risk Procedural Support



At risk (n)					
	With ECMO	46	32	31	28
	Without ECMO	25	7	7	7

Sheu et al (2010) **ECMO** assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound **cardiogenic shock**. Crit Care Med 38:1810.

eCPR
ECMO or ECLS supported Cardiovascular Arrest

After cardiac arrest
(E-CPR)---inhospital

Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest:
A comparison with conventional cardiopulmonary resuscitation

Crit Care Med 2011;39:1-7

Conclusions: Extracorporeal cardiopulmonary resuscitation showed a survival benefit (with "minimal neurologic impairment") over conventional cardiopulmonary resuscitation in patients who received cardiopulmonary resuscitation for >10 mins after witnessed in-hospital arrest, especially in cases with cardiac origins

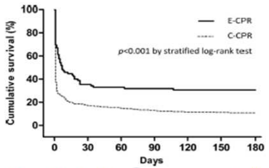


Figure 2. Kaplan-Meier curves of survival with minimal neurologic impairment for the study population. *E-CPR*, extracorporeal cardiopulmonary resuscitation; *C-CPR*, conventional cardiopulmonary resuscitation.

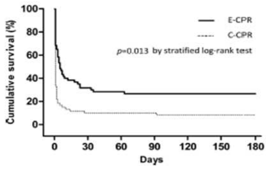
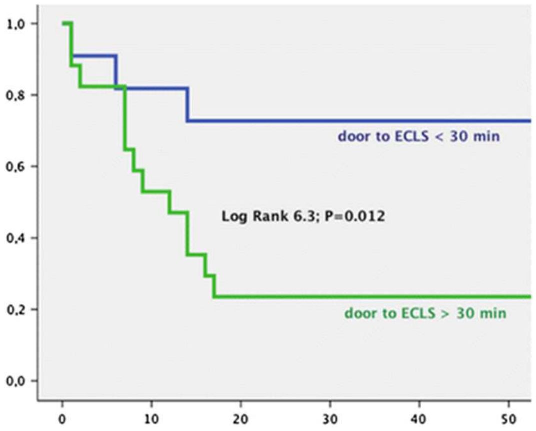


Figure 3. Kaplan-Meier curves of survival with minimal neurologic impairment for the propensity score-matched patients. *E-CPR*, extracorporeal cardiopulmonary resuscitation; *C-CPR*, conventional cardiopulmonary resuscitation.



The 30-day mortality rate in patients with witnessed OHCA undergoing ECLS treatment can be significantly improved if ECLS support is established within the first 30 min after admission …rdECMO

Leick et al (2013) Door-to-implantation time of extracorporeal life support systems predicts mortality in patients with out-of-hospital cardiac arrest. Clin Resarch Cardiol 102:661.

After cardiac arrest
(E-CPR)---out-of-hospital

Extracorporeal Cardiopulmonary Resuscitation for Patients With Out-of-Hospital Cardiac Arrest of Cardiac Origin: A Propensity-Matched Study and Predictor Analysis*

Maekawa et al. Crit Care Med 2013; 41:1186–1196

24 selected patients in each group:
ECPR vs CCPR , CPR > 20 min.
"Neurologically intact survival" 3M post arrest: 29% vs 8%
8/44 unmatched ECPR patients
# needed to treat: 5

Extracorporeal life support following out-of-hospital refractory cardiac arrest

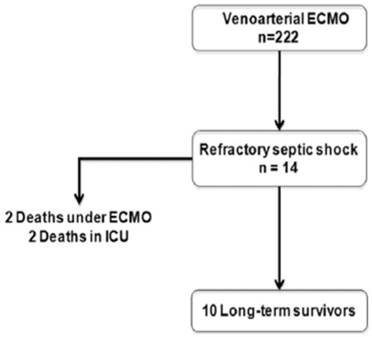
Le Guen et al. Critical Care 2011;15:R29

Witnessed, OH cardiac arrest
Refractory: no ROSC after 30 min CPR
51 patients, only 5 survived after 48 hr, 2 survived to 28 days

---

Mechanical Support in Sepsis

Venoarterial Extracorporeal Membrane Oxygenation Support for Refractory Cardiovascular Dysfunction During Severe Bacterial Septic Shock*

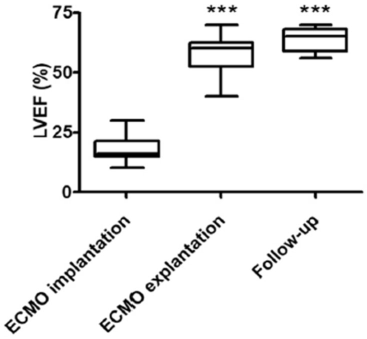


Venoarterial ECMO
n=222

Refractory septic shock
n = 14

2 Deaths under ECMO
2 Deaths in ICU

10 Long-term survivors



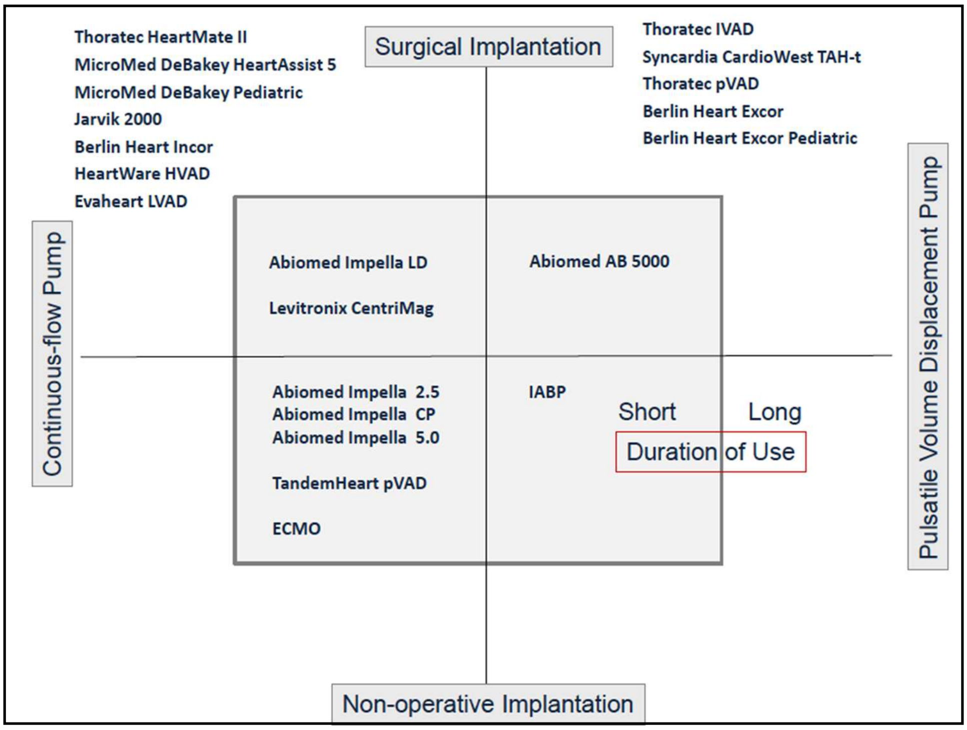
Crit Care Med 2013;41:1616-1626

Table 2. Hemodynamic effects of mechanical circulatory support devices.

	IABP	ECMO	TANDEM-HEART	IMPELLA
Afterload	Reduced	Increased	Increased	Neutral
LV stroke volume	Slight increase	Reduced	Reduced	Reduced
Coronary perfusion	Slight increase	Unknown	Unknown	Unknown
LV preload	Slightly reduced	Reduced	Reduced	Slightly reduced
PCWP	Slightly reduced	Reduced	Reduced	Slightly reduced
Peripheral tissue perfusion	No significant increase	Improved	Improved	Improved

Note: Adapted from Werdan K, Gielen S, Ebelt H and Hochman JS, "Mechanical circulatory support in cardiogenic shock," *European Heart Journal* (2014) 35, 156–67, by permission from Oxford University Press and European Society of Cardiology.

Ventricular Assist Devices



Thoracec HeartMate II
MicroMed DeBakey HeartAssist 5
MicroMed DeBakey Pediatric
Jarvik 2000
Berlin Heart Incor
HeartWare HVAD
Evaheart LVAD

Surgical Implantation

Thoratec IVAD
Syncardia CardioWest TAH-t
Thoratec pVAD
Berlin Heart Excor
Berlin Heart Excor Pediatric

Continuous-flow Pump

Pulsatile Volume Displacement Pump

Abiomed Impella LD
Levitronix CentriMag

Abiomed AB 5000

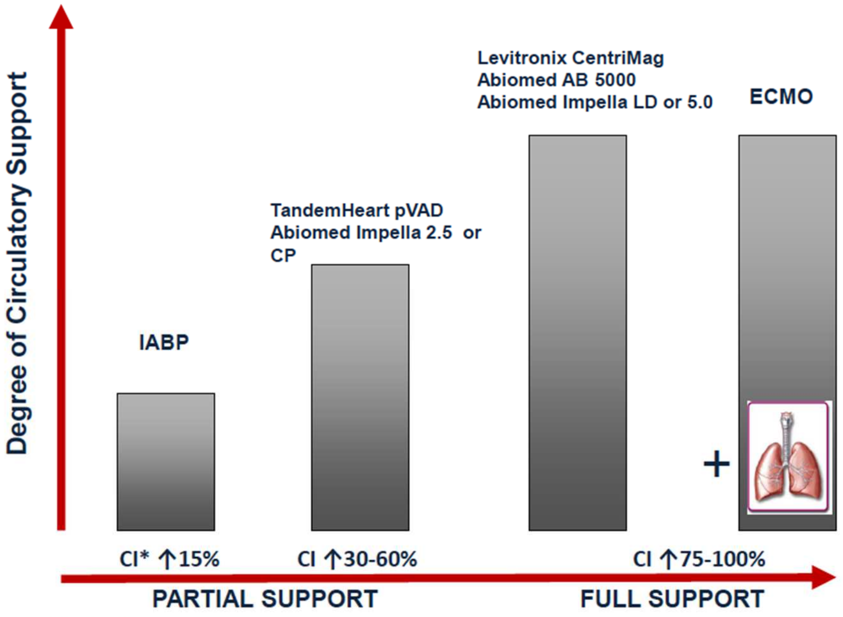
Abiomed Impella 2.5
Abiomed Impella CP
Abiomed Impella 5.0
TandemHeart pVAD
ECMO

IABP

Short
Long
Duration of Use

Non-operative Implantation

Temporary MCSD: Degree of Circulatory Support



Degree of Circulatory Support

IABP

TandemHeart pVAD
Abiomed Impella 2.5 or CP

Levitronix CentriMag
Abiomed AB 5000
Abiomed Impella LD or 5.0

ECMO

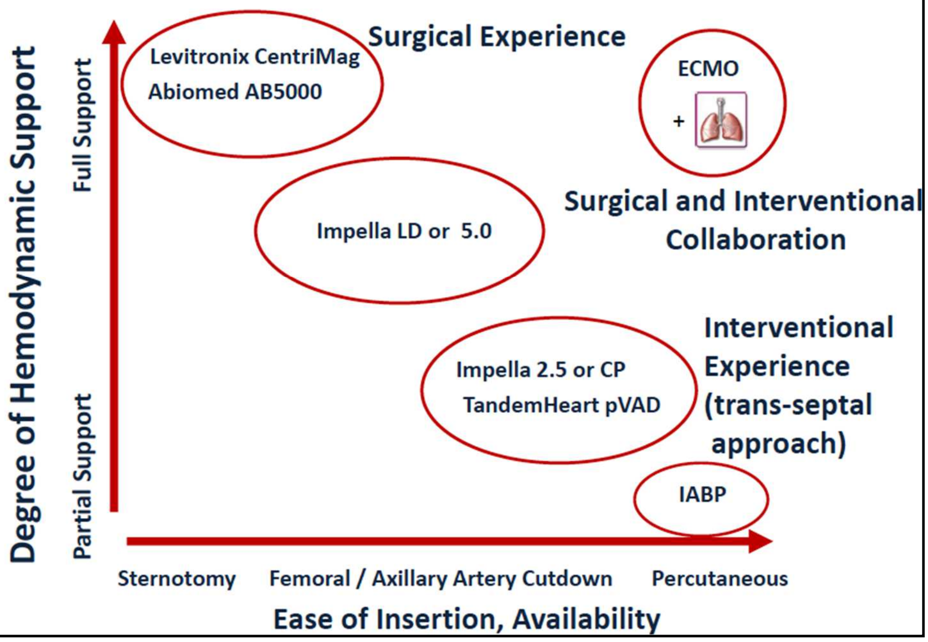
+

CI* ↑15% | CI ↑30-60% | CI ↑75-100%

PARTIAL SUPPORT | FULL SUPPORT

*CI – cardiac index

Temporary MCSD: Ease of Insertion



Degree of Hemodynamic Support

Full Support

Partial Support

Levitronix CentriMag
Abiomed AB5000

Surgical Experience

ECMO
+

Impella LD or 5.0

Surgical and Interventional Collaboration

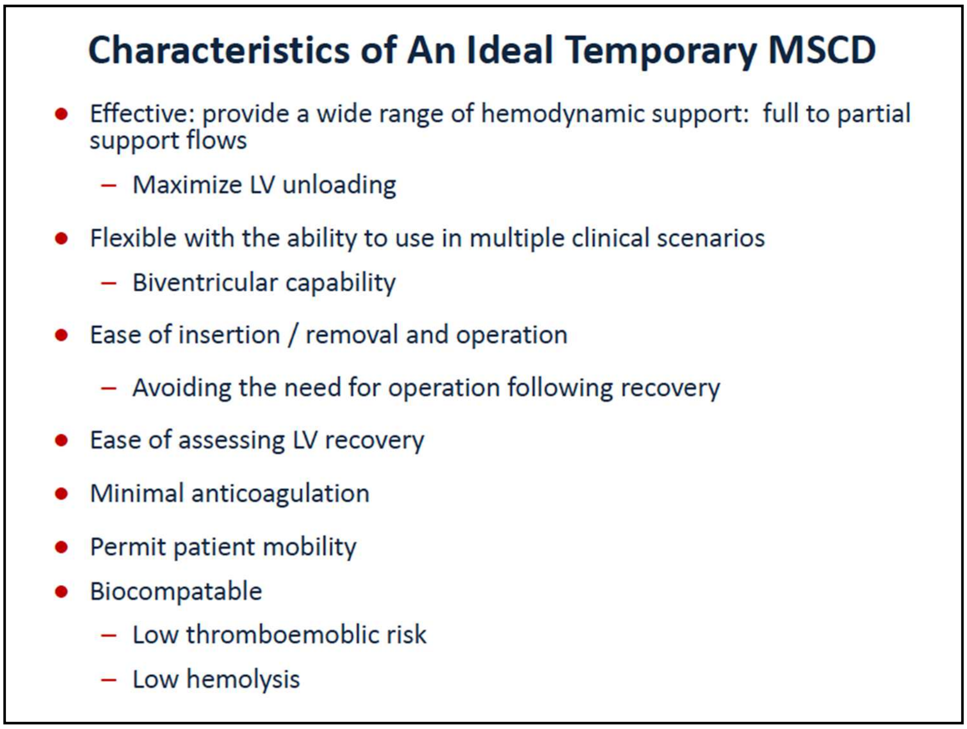
Impella 2.5 or CP
TandemHeart pVAD

Interventional Experience (trans-septal approach)

IABP

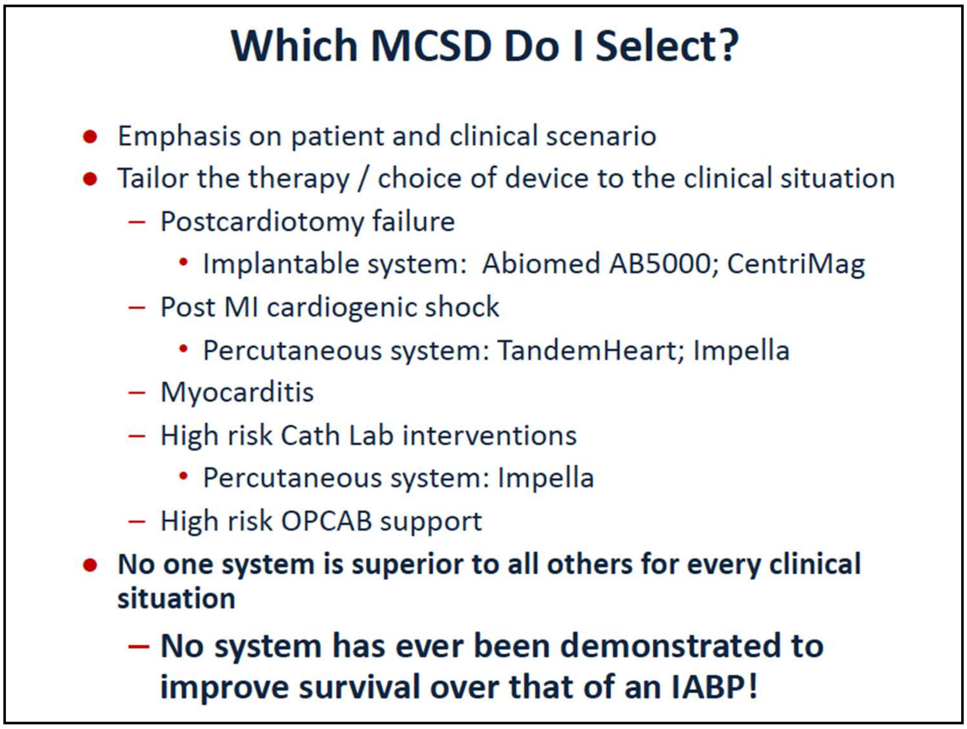
Sternotomy | Femoral / Axillary Artery Cutdown | Percutaneous

Ease of Insertion, Availability



Characteristics of An Ideal Temporary MSCD

- Effective: provide a wide range of hemodynamic support: full to partial support flows
  - Maximize LV unloading
- Flexible with the ability to use in multiple clinical scenarios
  - Biventricular capability
- Ease of insertion / removal and operation
  - Avoiding the need for operation following recovery
- Ease of assessing LV recovery
- Minimal anticoagulation
- Permit patient mobility
- Biocompatable
  - Low thromboemoblic risk
  - Low hemolysis



Which MCSD Do I Select?

- Emphasis on patient and clinical scenario
- Tailor the therapy / choice of device to the clinical situation
  - Postcardiotomy failure
    - Implantable system: Abiomed AB5000; CentriMag
  - Post MI cardiogenic shock
    - Percutaneous system: TandemHeart; Impella
  - Myocarditis
  - High risk Cath Lab interventions
    - Percutaneous system: Impella
  - High risk OPCAB support
- **No one system is superior to all others for every clinical situation**
  - **No system has ever been demonstrated to improve survival over that of an IABP!**

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American
Heart
Association.

A Prospective, Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention : The PROTECT II Study

William W. O'Neill, Neal S. Kleiman, Jeffrey Moses, Jose P.S. Henriques, Simon Dixon, Joseph Massaro, Igor Palacios, Brijeshwar Maini, Suresh Mulukutla, Vladimír Dzavík, Jeffrey Popma, Pamela S. Douglas and Magnus Ohman

Circulation. 2012 Oct 2;126(14):1717-27.

Conclusions:

The 30-day incidence of major adverse events was not different for patients with IABP or Impella 2.5 hemodynamic support. However, trends for improved outcomes were observed for Impella 2.5–supported patients at 90 days.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 4, 2012 VOL. 367 NO. 14

Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock

Holger Thiele, M.D., Uwe Zeymer, M.D., Franz-Josef Neumann, M.D., Miroslaw Ferenc, M.D., Hans-Georg Olbrich, M.D., Jörg Hausleiter, M.D., Gert Richardt, M.D., Marcus Hennersdorf, M.D., Klaus Empen, M.D., Georg Fuernau, M.D., Steffen Desch, M.D., Ingo Eitel, M.D., Rainer Hambrecht, M.D., Jörg Fuhrmann, M.D., Michael Böhm, M.D., Henning Ebelt, M.D., Steffen Schneider, Ph.D., Gerhard Schuler, M.D., and Karl Werdan, M.D., for the IABP-SHOCK II Trial Investigators*

Conclusions:

The use of intraaortic balloon counterpulsation did not significantly reduce 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction for whom an early revascularization strategy was planned.

EUROPEAN SOCIETY OF CARDIOLOGY®
European Heart Journal (2009) **30**, 2102–2108
doi:10.1093/eurheartj/ehp292

CLINICAL RESEARCH
Coronary heart disease

Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials

Jin M. Cheng, Corstiaan A. den Uil*, Sanne E. Hoeks, Martin van der Ent, Lucia S.D. Jewbali, Ron T. van Domburg, and Patrick W. Serruys

CONCLUSIONS:

Although percutaneous LVAD provides superior hemodynamic support in patients with cardiogenic shock compared with IABP, the use of these more powerful devices did not improve early survival. These results do not yet support percutaneous LVAD as first-choice approach in the mechanical management of cardiogenic shock.

Common Pitfalls to Temporary MCS

Maximum MCS in terms of flow ≠ Maximum LV decompression:

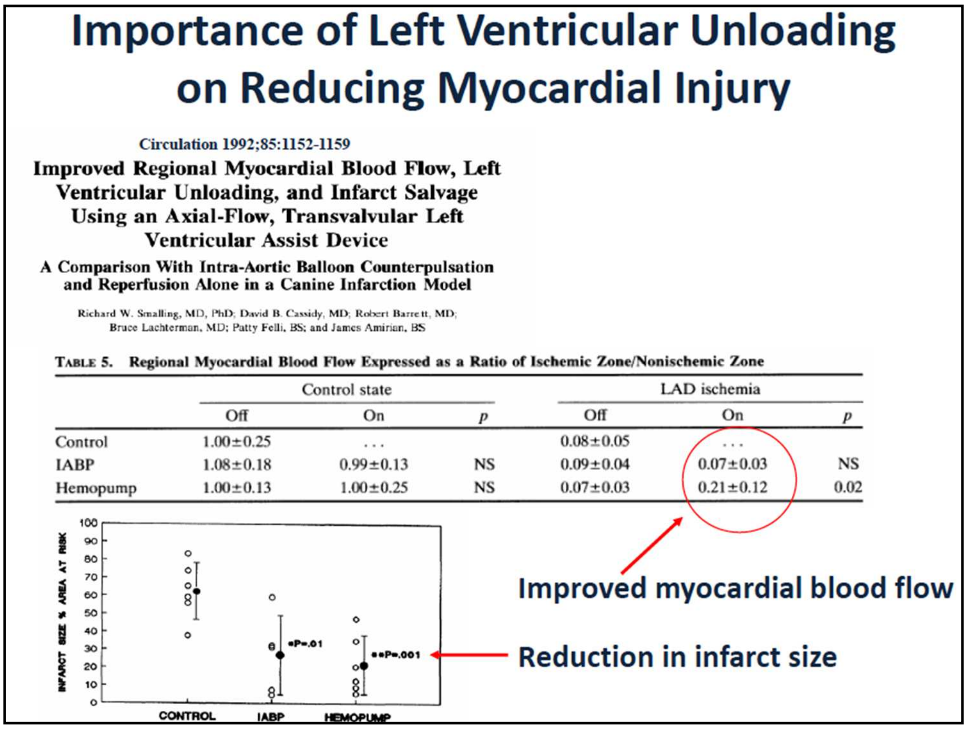
- not optimizing LV decompression for LV recovery
- increasing the thromboembolic risk – LV thrombus from stasis

Direct Unloading of the LV

- Apical cannulation
  - Abiomed AB5000
  - Levitronix CentriMag
- RSPV with catheter placement across MV
  - Limits assessment of recovery
- Impella LD or 5.0
- Impella 2.5 or CP

Indirect Unloading of the LV

- ECMO
- TandemHeart
- IABP



Importance of Left Ventricular Unloading on Reducing Myocardial Injury

Circulation 1992;85:1152-1159

Improved Regional Myocardial Blood Flow, Left Ventricular Unloading, and Infarct Salvage Using an Axial-Flow, Transvalvular Left Ventricular Assist Device

A Comparison With Intra-Aortic Balloon Counterpulsation and Reperfusion Alone in a Canine Infarction Model

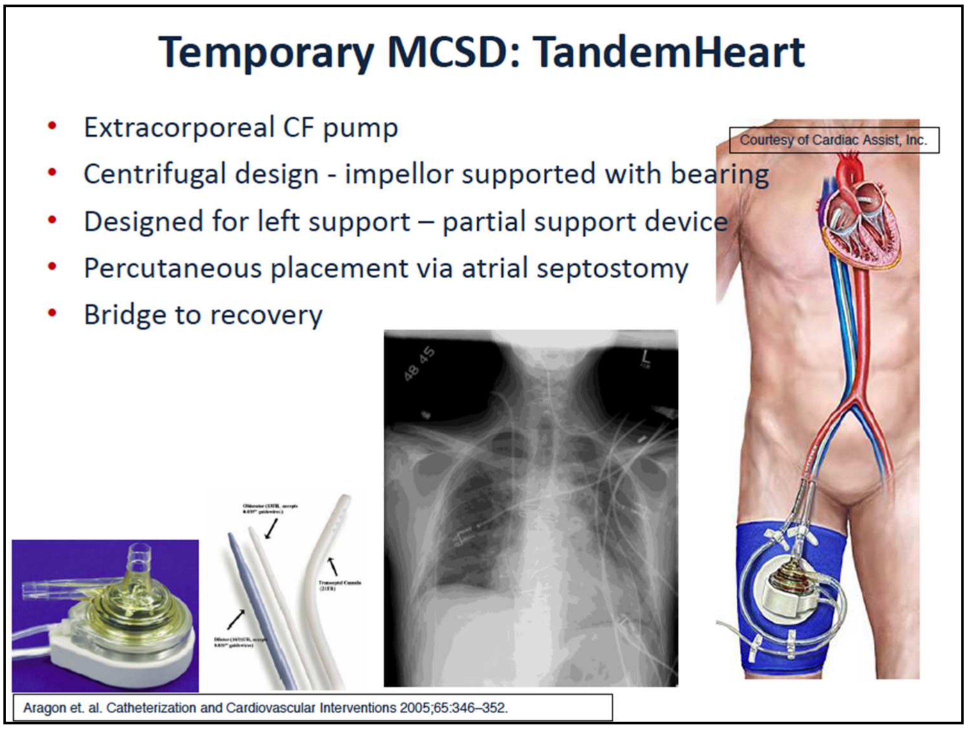
Richard W. Smalling, MD, PhD; David B. Cassidy, MD; Robert Barrett, MD;
Bruce Lachterman, MD; Patty Felli, BS; and James Amirian, BS

Table 5. Regional Myocardial Blood Flow Expressed as a Ratio of Ischemic Zone/Nonischemic Zone

	Control state			LAD ischemia		
	Off	On	*p*	Off	On	*p*
Control	1.00±0.25	. . .		0.08±0.05	. . .	
IABP	1.08±0.18	0.99±0.13	NS	0.09±0.04	0.07±0.03	NS
Hemopump	1.00±0.13	1.00±0.25	NS	0.07±0.03	0.21±0.12	0.02

Improved myocardial blood flow

Reduction in infarct size



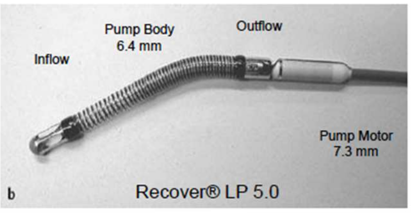
Temporary MCSD: TandemHeart

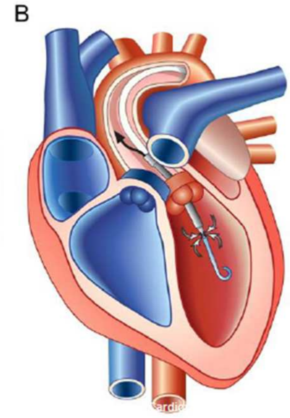
- Extracorporeal CF pump
- Centrifugal design - impellor supported with bearing
- Designed for left support – partial support device
- Percutaneous placement via atrial septostomy
- Bridge to recovery

Courtesy of Cardiac Assist, Inc.

Aragon et. al. Catheterization and Cardiovascular Interventions 2005;65:346–352.

Temporary MCSD: Impella





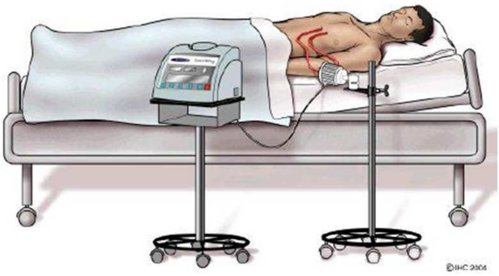
- CF pump with axial design
- Designed for left support – partial support device
- Percutaneous or surgical implantation
- Bridge to recovery

Table 2. Hemodynamic effects of mechanical circulatory support devices.

	IABP	ECMO	TANDEM-HEART	IMPELLA
Afterload	Reduced	Increased	Increased	Neutral
LV stroke volume	Slight increase	Reduced	Reduced	Reduced
Coronary perfusion	Slight increase	Unknown	Unknown	Unknown
LV preload	Slightly reduced	Reduced	Reduced	Slightly reduced
PCWP	Slightly reduced	Reduced	Reduced	Slightly reduced
Peripheral tissue perfusion	No significant increase	Improved	Improved	Improved

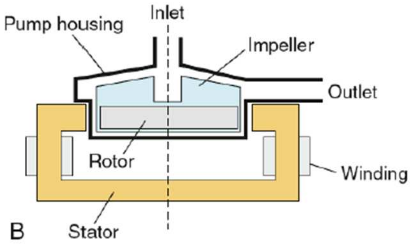
Note: Adapted from Werdan K, Gielen S, Ebelt H and Hochman JS, "Mechanical circulatory support in cardiogenic shock," *European Heart Journal* (2014) 35, 156–67, by permission from Oxford University Press and European Society of Cardiology.

Temporary MCSD: Levitronix CentriMag



Courtesy of Levitronix, Inc.

- Extracorporeal CF rotary pump
- Centrifugal design
- Magnetically-levitated
- Left, Right, or Biventricular support – full support device
- Operative placement requiring sternotomy
- Bridge to recovery



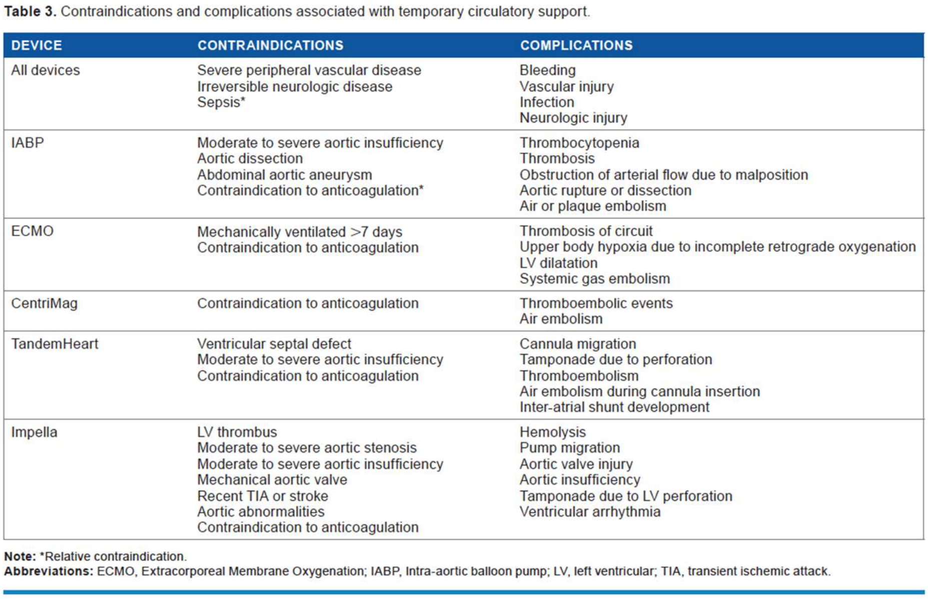
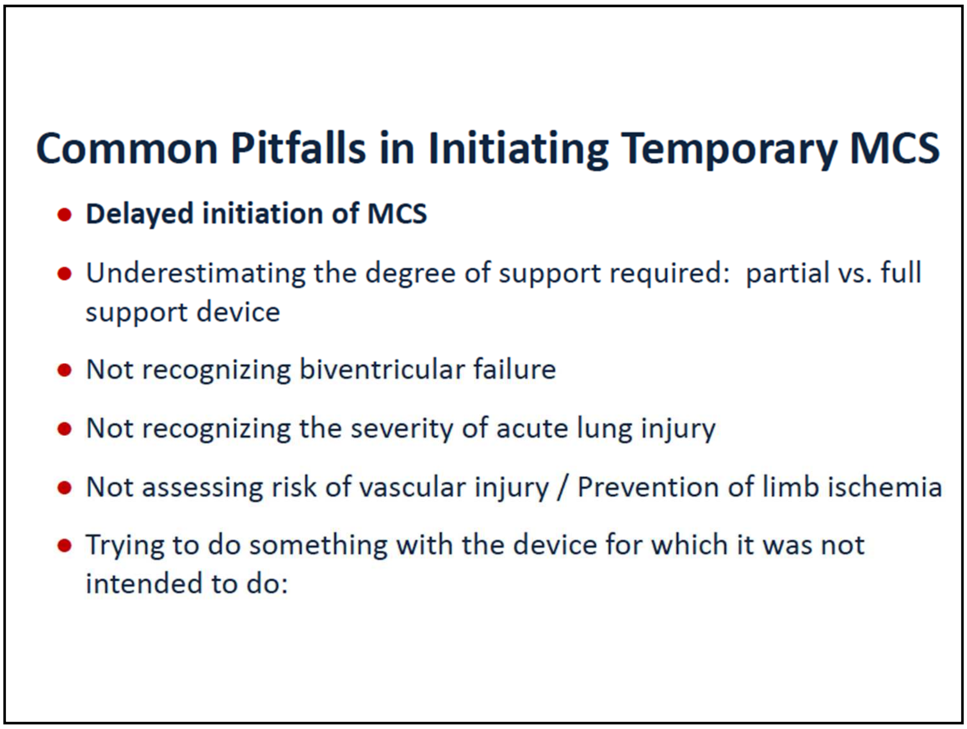


Table 3. Contraindications and complications associated with temporary circulatory support.

DEVICE	CONTRAINDICATIONS	COMPLICATIONS
All devices	Severe peripheral vascular disease Irreversible neurologic disease Sepsis*	Bleeding Vascular injury Infection Neurologic injury
IABP	Moderate to severe aortic insufficiency Aortic dissection Abdominal aortic aneurysm Contraindication to anticoagulation*	Thrombocytopenia Thrombosis Obstruction of arterial flow due to malposition Aortic rupture or dissection Air or plaque embolism
ECMO	Mechanically ventilated >7 days Contraindication to anticoagulation	Thrombosis of circuit Upper body hypoxia due to incomplete retrograde oxygenation LV dilatation Systemic gas embolism
CentriMag	Contraindication to anticoagulation	Thromboembolic events Air embolism
TandemHeart	Ventricular septal defect Moderate to severe aortic insufficiency Contraindication to anticoagulation	Cannula migration Tamponade due to perforation Thromboembolism Air embolism during cannula insertion Inter-atrial shunt development
Impella	LV thrombus Moderate to severe aortic stenosis Moderate to severe aortic insufficiency Mechanical aortic valve Recent TIA or stroke Aortic abnormalities Contraindication to anticoagulation	Hemolysis Pump migration Aortic valve injury Aortic insufficiency Tamponade due to LV perforation Ventricular arrhythmia

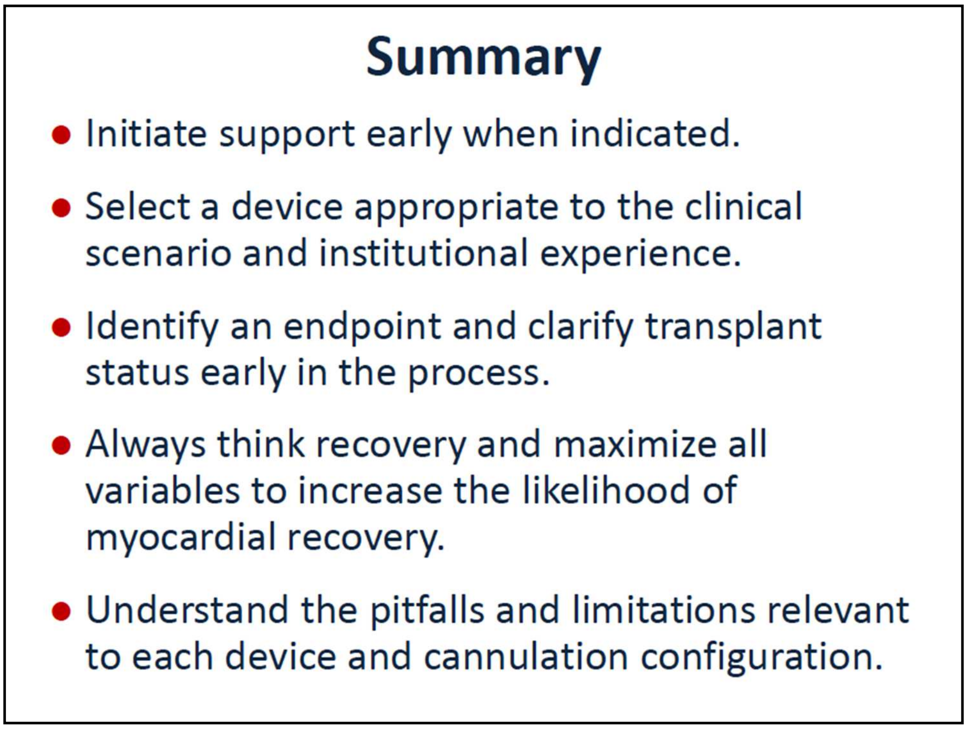
Note: *Relative contraindication.
Abbreviations: ECMO, Extracorporeal Membrane Oxygenation; IABP, Intra-aortic balloon pump; LV, left ventricular; TIA, transient ischemic attack.

Gilotra et al, Clin Med Ins, Card, 2014:8



Common Pitfalls in Initiating Temporary MCS

- **Delayed initiation of MCS**
- Underestimating the degree of support required: partial vs. full support device
- Not recognizing biventricular failure
- Not recognizing the severity of acute lung injury
- Not assessing risk of vascular injury / Prevention of limb ischemia
- Trying to do something with the device for which it was not intended to do:



Summary

- Initiate support early when indicated.
- Select a device appropriate to the clinical scenario and institutional experience.
- Identify an endpoint and clarify transplant status early in the process.
- Always think recovery and maximize all variables to increase the likelihood of myocardial recovery.
- Understand the pitfalls and limitations relevant to each device and cannulation configuration.

THANK YOU

- QUESTIONS?

Ultrasound in the ICU: What Every Intensivist Should Know

Raghu R. Seethala, MD
Instructor of Emergency Medicine

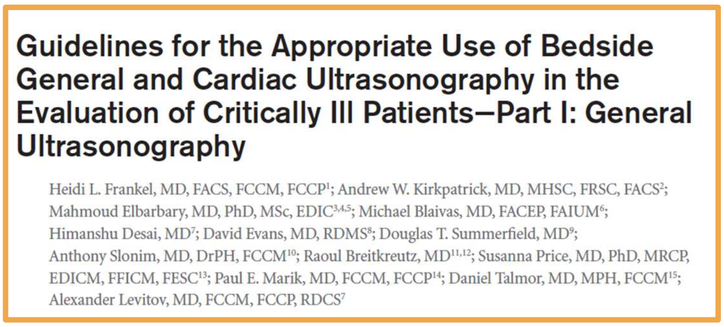
Conflict of interest disclosures

- None

Learning objectives

- Discuss the utility and various applications of bedside ultrasound in the intensive care unit
- Provide a brief overview regarding the types of ultrasound intensivists should be familiar with including:
  - Cardiac
  - Thoracic
  - Abdominal
  - Vascular
  - Procedural

Society of Critical Care Medicine
The Intensive Care Professionals



Guidelines for the Appropriate Use of Bedside General and Cardiac Ultrasonography in the Evaluation of Critically Ill Patients—Part I: General Ultrasonography

Heidi L. Frankel, MD, FACS, FCCM, FCCP[1]; Andrew W. Kirkpatrick, MD, MHSC, FRSC, FACS[2]; Mahmoud Elbarbary, MD, PhD, MSc, EDIC[3,4,5]; Michael Blaivas, MD, FACEP, FAIUM[6]; Himanshu Desai, MD[7]; David Evans, MD, RDMS[8]; Douglas T. Summerfield, MD[9]; Anthony Slonim, MD, DrPH, FCCM[10]; Raoul Breitkreutz, MD[11,12]; Susanna Price, MD, PhD, MRCP, EDICM, FFICM, FESC[13]; Paul E. Marik, MD, FCCM, FCCP[14]; Daniel Talmor, MD, MPH, FCCM[15]; Alexander Levitov, MD, FCCM, FCCP, RDCS[7]

Accreditation Council for
Graduate Medical Education

- Anesthesiology Critical Care Medicine
- Internal Medicine Critical Care Medicine
- Pulmonary Critical Care Medicine
- Surgical Critical Care

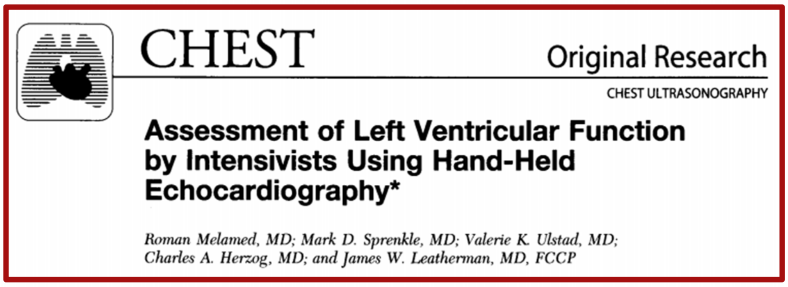
Benefits

- Can be obtained real-time
- The treating physician is the one performing ad interpreting the scan, therefore they can incorporate other clinical data to understand the clinical scenario better
- Can be repeated as often as needed to monitor treatment effects

Pitfalls

- Inadequate views
- Operator dependent
- Incorrect interpretation

- Can intensivists competently perform bedside ultrasound?
- Is it helpful in the management of ICU patients?



CHEST

Original Research

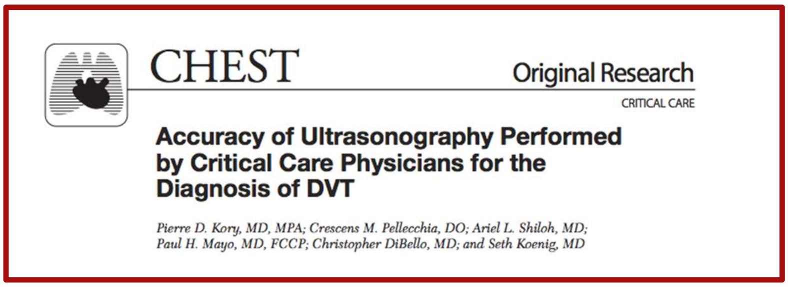
CHEST ULTRASONOGRAPHY

Assessment of Left Ventricular Function by Intensivists Using Hand-Held Echocardiography*

Roman Melamed, MD; Mark D. Sprenkle, MD; Valerie K. Ulstad, MD; Charles A. Herzog, MD; and James W. Leatherman, MD, FCCP

- Intensivists correctly identified:
  - – normal LV function in 22 of 24 cases (92%)
  - – abnormal LV function in 16 of 20 cases (80%)
- The K statistic for the agreement between intensivist and echocardiographer for any abnormality in LV function was 0.72

Chest. 2009 Jun;135(6):1416-20



CHEST

Original Research

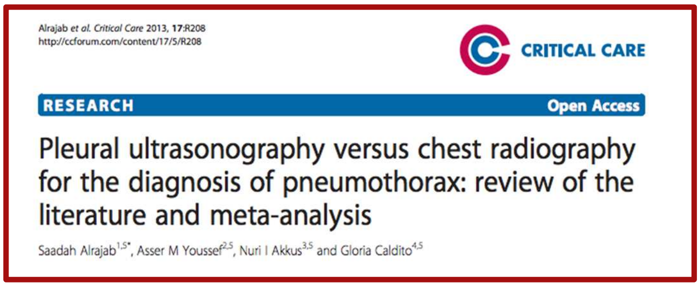
CRITICAL CARE

Accuracy of Ultrasonography Performed by Critical Care Physicians for the Diagnosis of DVT

Pierre D. Kory, MD, MPA; Crescens M. Pellecchia, DO; Ariel L. Shiloh, MD; Paul H. Mayo, MD, FCCP; Christopher DiBello, MD; and Seth Koenig, MD

- Sensitivity of 86%
- Specificity of 96%
- Diagnostic accuracy of 95%

Chest. 2011 Mar;139(3):538-42



Alrajab *et al. Critical Care* 2013, **17**:R208
http://ccforum.com/content/17/5/R208

CRITICAL CARE

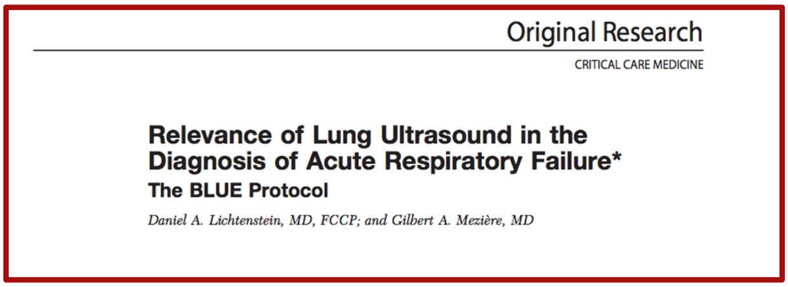
RESEARCH **Open Access**

Pleural ultrasonography versus chest radiography for the diagnosis of pneumothorax: review of the literature and meta-analysis

Saadah Alrajab[1,5*], Asser M Youssef[2,5], Nuri I Akkus[3,5] and Gloria Caldito[4,5]

- Ultrasound
  - – sensitivity of 78.6% (95% CI, 68.1 to 98.1)
  - – specificity of 98.4% (95% CI, 97.3 to 99.5)
- Chest radiography
  - – Sensitivity 39.8% (95% CI, 29.4 to 50.3)
  - – specificity of 99.3% (95% CI, 98.4 to 100)

Crit Care. 2013 Sep 23;17(5):R208



Original Research

CRITICAL CARE MEDICINE

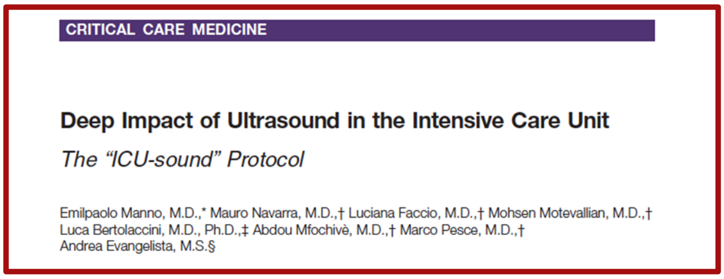
Relevance of Lung Ultrasound in the Diagnosis of Acute Respiratory Failure*

The BLUE Protocol

Daniel A. Lichtenstein, MD, FCCP; and Gilbert A. Mezière, MD

- The use of the BLUE protocol would have provided correct diagnoses in 90.5% of cases

Chest. 2008 Jul;134(1):117-25



CRITICAL CARE MEDICINE

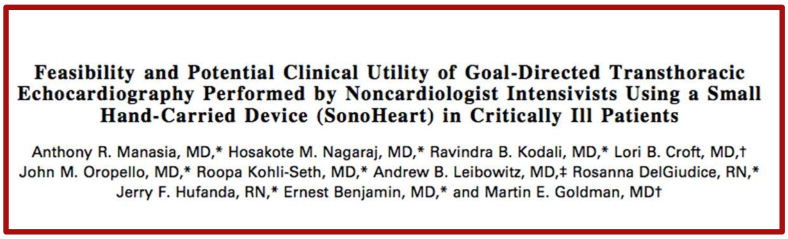
Deep Impact of Ultrasound in the Intensive Care Unit

The "ICU-sound" Protocol

Emilpaolo Manno, M.D.,* Mauro Navarra, M.D.,† Luciana Faccio, M.D.,† Mohsen Motevallian, M.D.,†
Luca Bertolaccini, M.D., Ph.D.,‡ Abdou Mfochivè, M.D.,† Marco Pesce, M.D.,†
Andrea Evangelista, M.S.§

- Modified the admitting diagnosis in 32/125 patients (25.6%)
- Confirmed it in 73/125 patients (58.4%)
- Not effective in confirming or modifying it in 17/125 patients (13.6%)
- Missed it in 3/125 patients (2.4%)
- Prompted further testing in 23/125 patients (18.4%)
- Led to changes in medical therapy in 22/125 patients (17.6%)
- Led to invasive procedures in 27/125 patients (21.6%)

Anesthesiology. 2012 Oct;117(4):801-9



Feasibility and Potential Clinical Utility of Goal-Directed Transthoracic Echocardiography Performed by Noncardiologist Intensivists Using a Small Hand-Carried Device (SonoHeart) in Critically Ill Patients

Anthony R. Manasia, MD,* Hosakote M. Nagaraj, MD,* Ravindra B. Kodali, MD,* Lori B. Croft, MD,†
John M. Oropello, MD,* Roopa Kohli-Seth, MD,* Andrew B. Leibowitz, MD,‡ Rosanna DelGiudice, RN,*
Jerry F. Hufanda, RN,* Ernest Benjamin, MD,* and Martin E. Goldman, MD†

- Intensivists successfully performed a diagnostic limited TTE in 94% of patients and interpreted their studies correctly in 84%
- Limited TTE provided new cardiac information and changed management in 37% of patients.
- TTE added useful information in an additional 47% of patients but did not alter immediate management

J Cardiothorac Vasc Anesth. 2005 Apr;19(2):155-9

Critical Care Ultrasound

- Cardiac
  - Basic
  - Advanced
- Thoracic
  - Pleura
  - Lung
- Vascular
- Abdominal
- Procedural

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Basic critical care echocardiography

- Global LV size and function
- Global RV size and function
- Volume status, LV and RV filling, IVC variability and size
- Pericardial effusion
- Pericardial tamponade
- Gross valvular abnormalities

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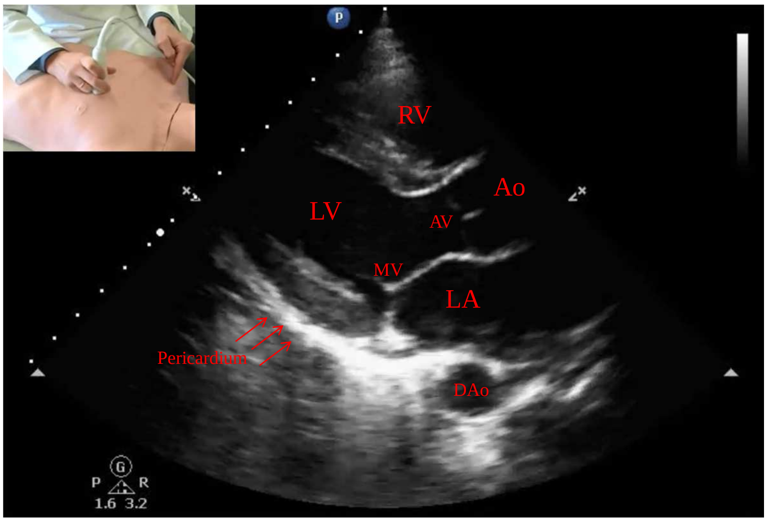
HARVARD MEDICAL SCHOOL

Parasternal long-axis


P
RV
Ao
LV
AV
MV
LA
Pericardium
DAo
G
P R
1.6 3.2

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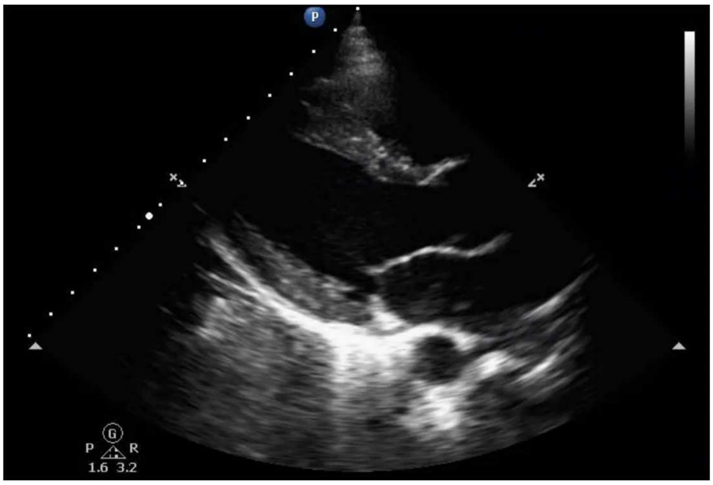
Parasternal long-axis



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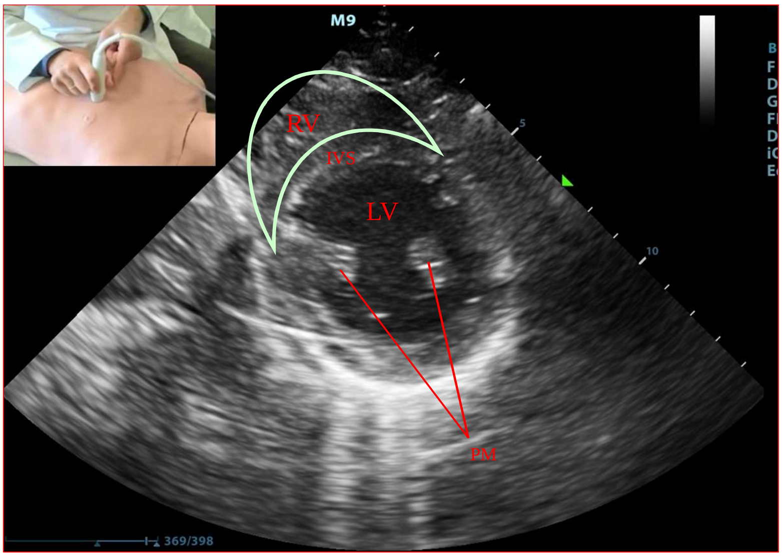
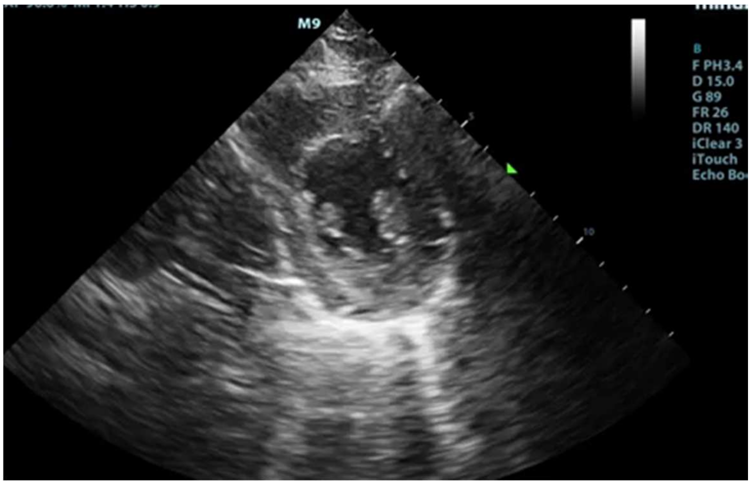
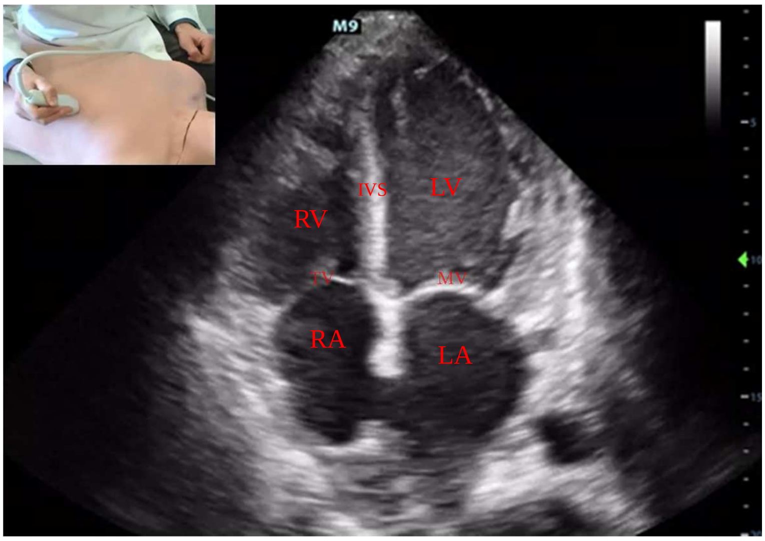
Parasternal short-axis


M9
RV
IVS
LV
PM
5
10
369/398

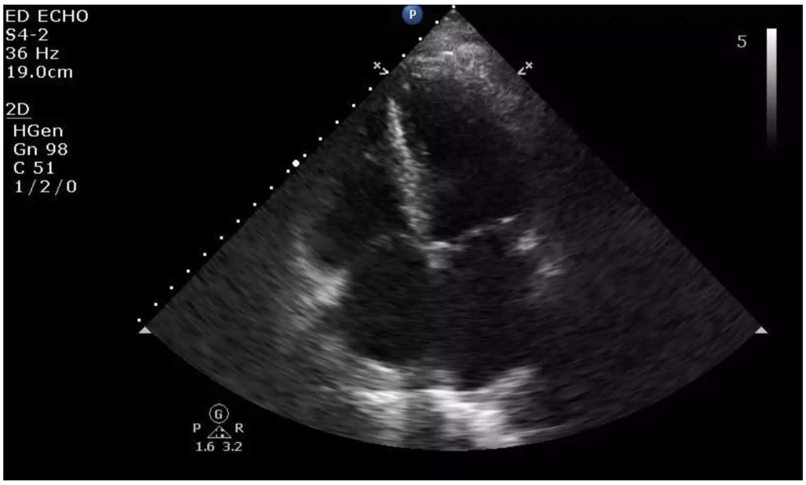
Parasternal long-axis


M9
B
F PH3.4
D 15.0
G 89
FR 26
DR 140
iClear 3
iTouch
Echo Bo
5
10

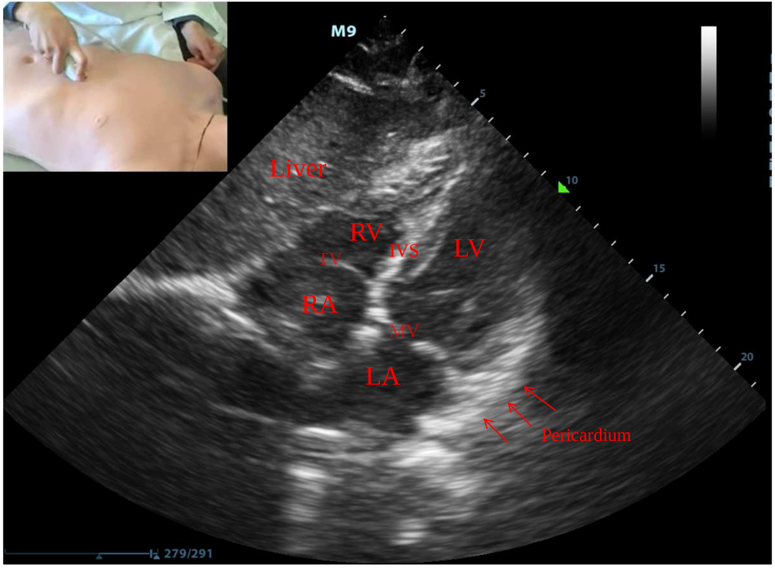
Apical 4-chamber


M9
IVS
LV
RV
TV
MV
RA
LA

Apical 4-chamber


ED ECHO
S4-2
36 Hz
19.0cm
2D
HGen
Gn 98
C 51
1/2/0
P
5
G
P R
1.6 3.2

Subcostal long-axis


M9
5
10
15
20
Liver
RV
TV
IVS
LV
RA
MV
LA
Pericardium
279/291

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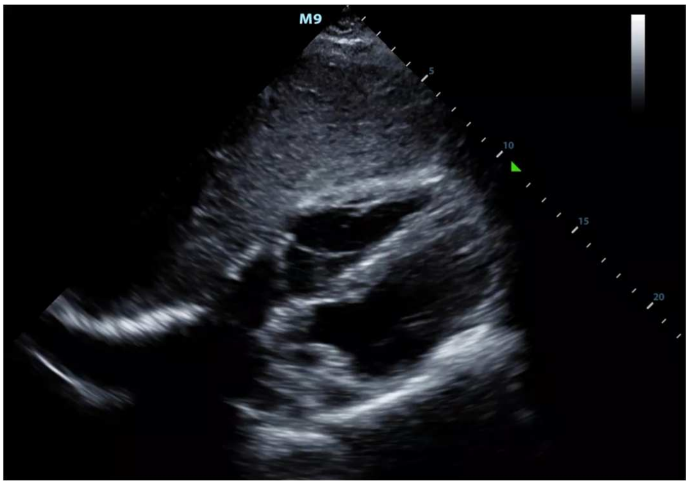
Subcostal long-axis



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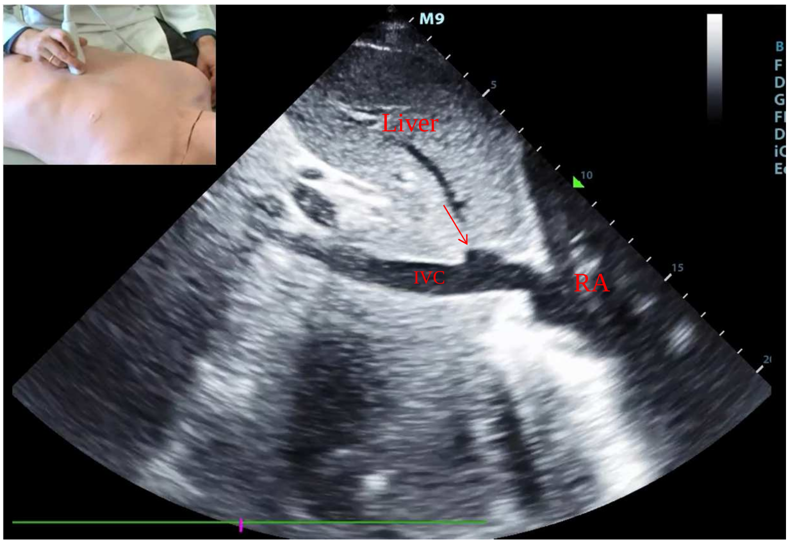
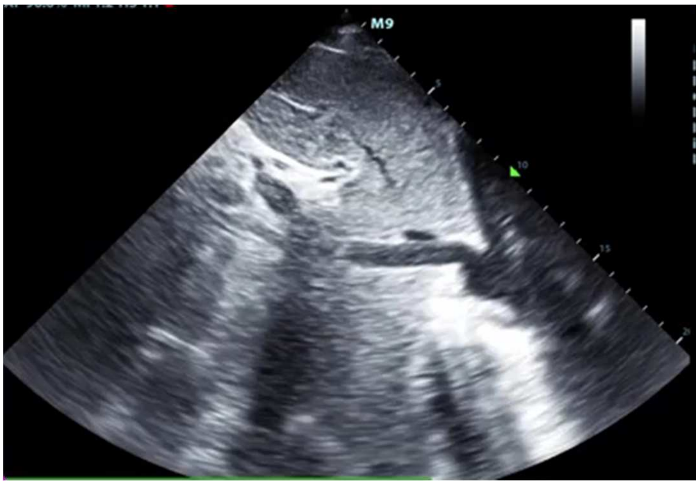
IVC



IVC evaluation for fluid responsiveness

- Best studied in mechanically ventilated, fully sedated patients without any spontaneous respirations
  - Respiratory variation greater then **12 – 18%** predicts volume responsiveness
- Spontaneously breathing patients
  - No great studies exist
  - However is a good estimate for CVP and some clinicians suggest:
    - **IVC < 2 cm**, greater than **50% collapse** with respiration suggests fluid responsiveness

Hypovolemia



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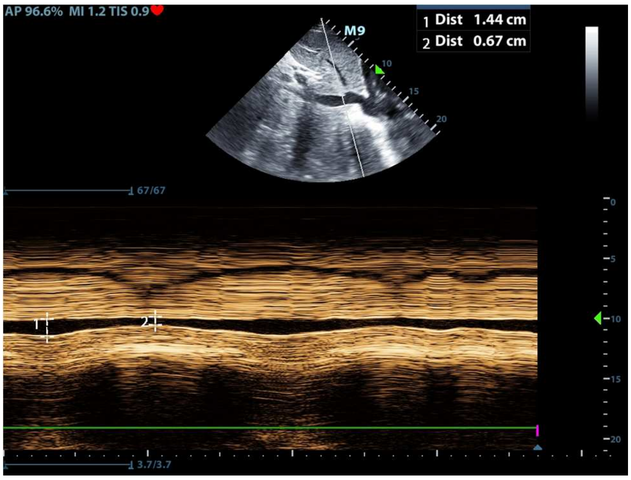
Hypovolemia


AP 96.6% MI 1.2 TIS 0.9
M9
1 Dist 1.44 cm
2 Dist 0.67 cm
10
15
20
67/67
0
5
10
15
20
1
2
3.7/3.7

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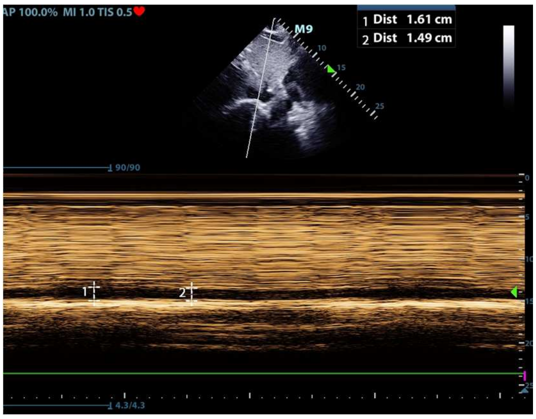
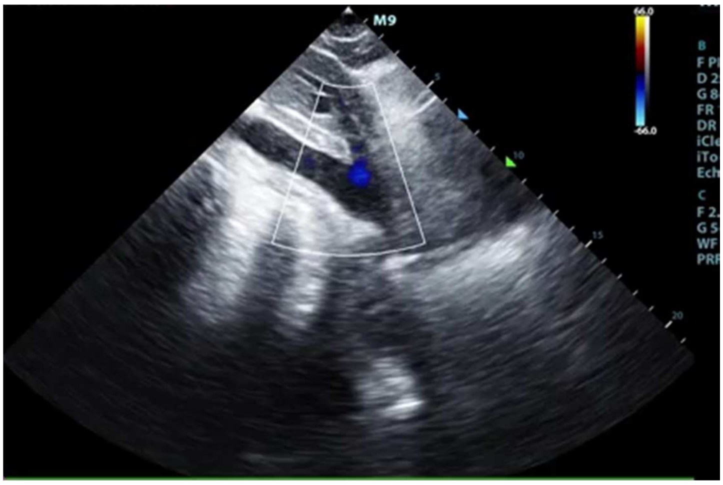
Normal IVC

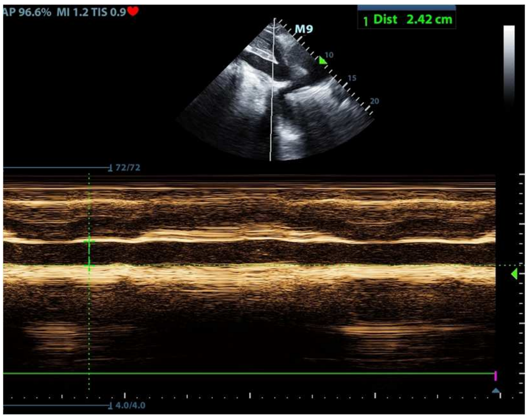

AP 100.0% MI 1.0 TIS 0.5
M9
1 Dist 1.61 cm
2 Dist 1.49 cm
90/90
4.3/4.3
1
2

Volume overloaded IVC

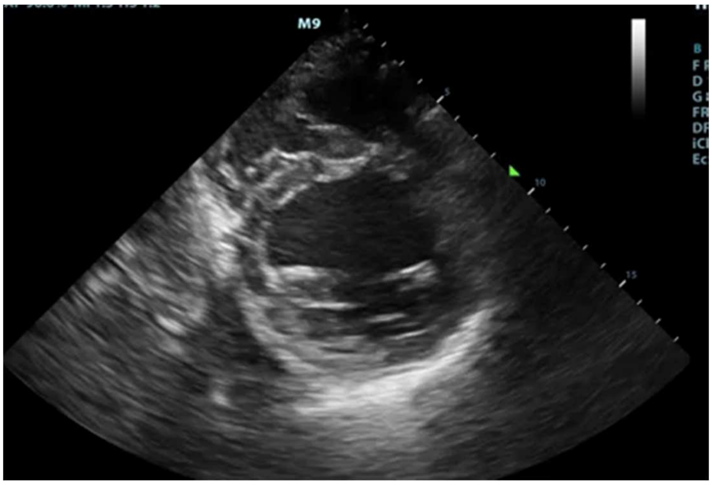

M9
66.0
-66.0
5
10
15
20

Volume overloaded IVC

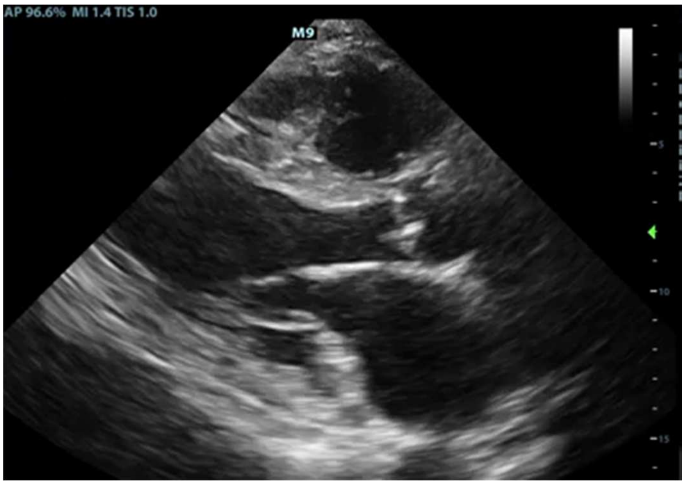
- > 2 cm
- No respiratory variation


AP 96.6% MI 1.2 TIS 0.9
M9
1 Dist 2.42 cm
10
15
20
72/72
4.0/4.0

Depressed LV function



Depressed LV function


AP 96.6% MI 1.4 TIS 1.0
M9
5
10
15

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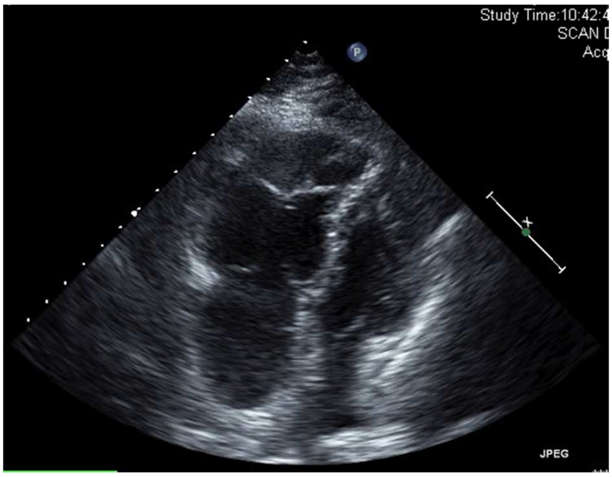
RV Strain


Study Time:10:42:4
SCAN D
Acq
P
JPEG

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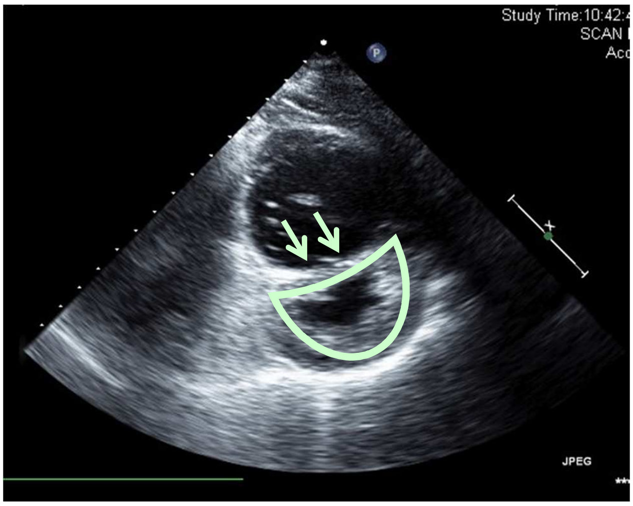
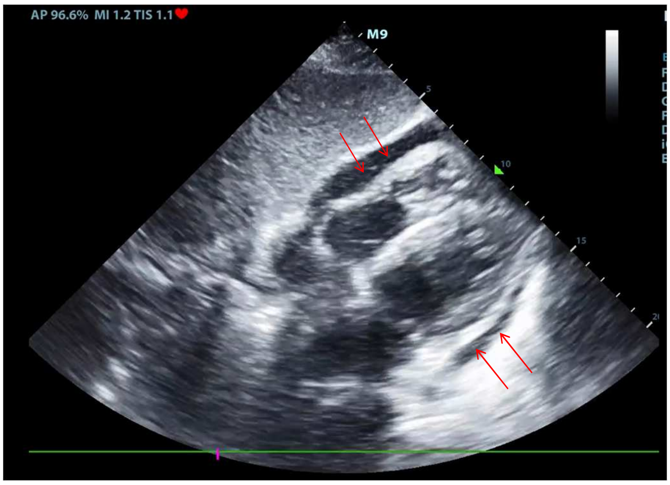
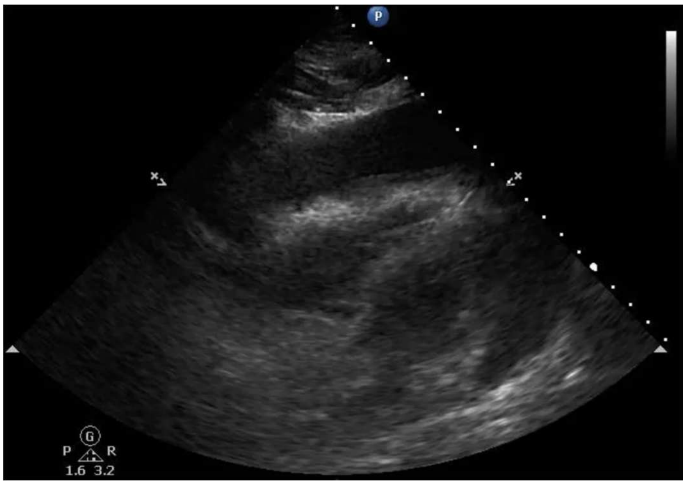
RV Strain


Study Time:10:42:
SCAN
Acc
P
JPEG

Pericardial Effusion


AP 96.6% MI 1.2 TIS 1.1
M9
5
10
15

Tamponade



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Thoracic Ultrasound

- Pleural effusion/ hemothorax
- Pneumothorax
- Lung consolidation
- Interstitial edema

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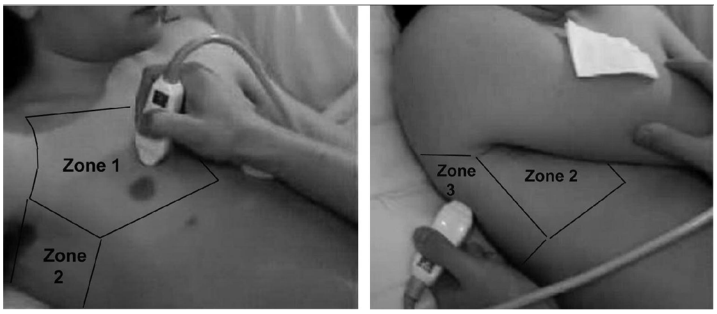
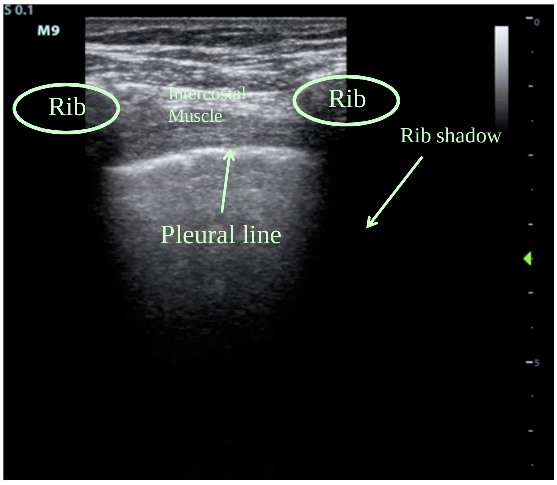
Basic views

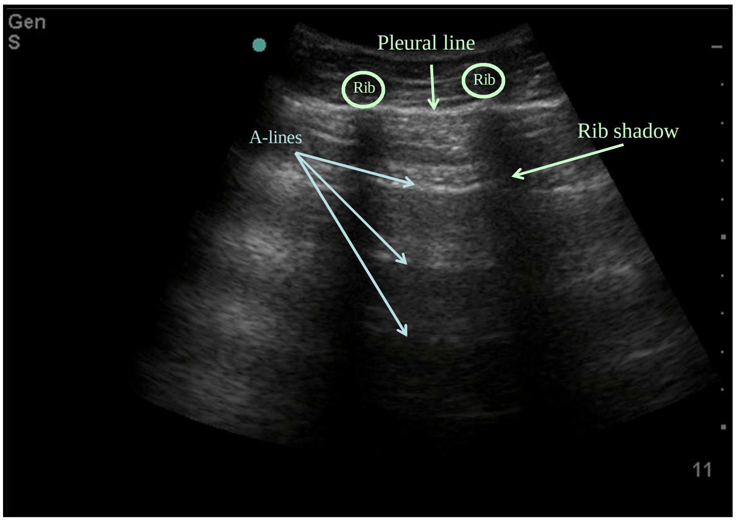

Zone 1
Zone 2
Zone 3
Zone 2

Chest. 2008 Jul;134(1):117-25

Normal lung


S 0.1
M9
Rib
Intercostal Muscle
Rib
Rib shadow
Pleural line

Normal lung


Gen
S
Pleural line
Rib
Rib
A-lines
Rib shadow
11

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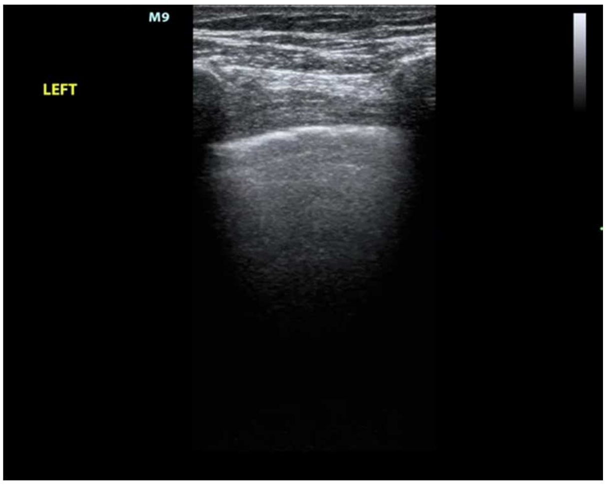
HARVARD MEDICAL SCHOOL

Lung sliding



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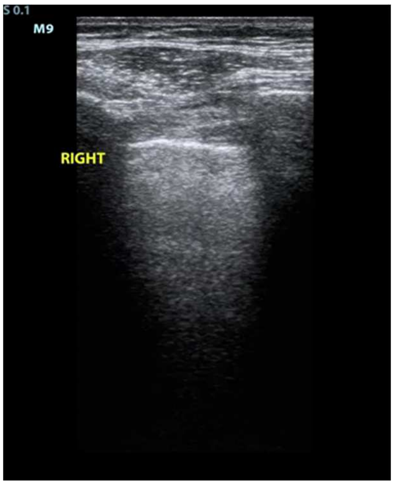
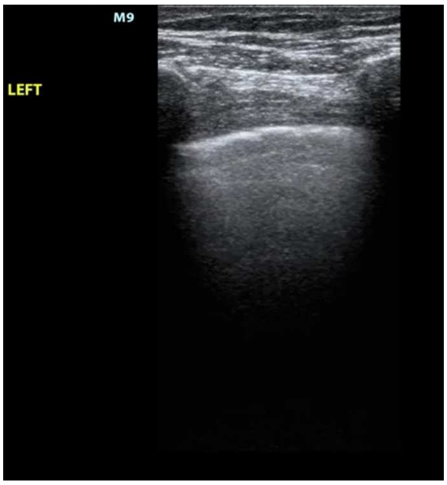
Pneumothorax


S 0.1
M9
RIGHT



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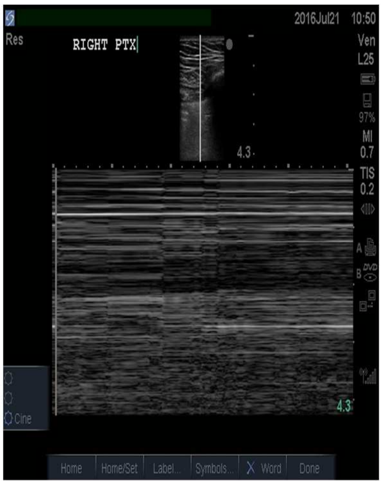
HARVARD MEDICAL SCHOOL

Pneumothorax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Res
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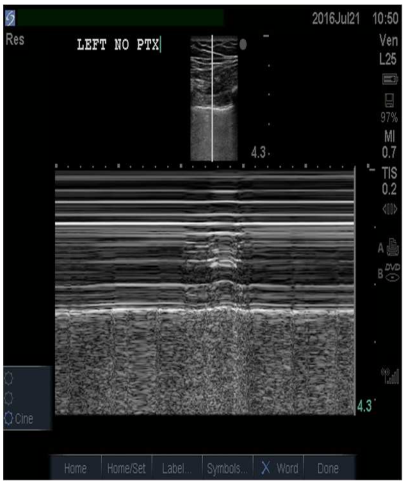
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BRIGHAM AND WOMEN'S HOSPITAL
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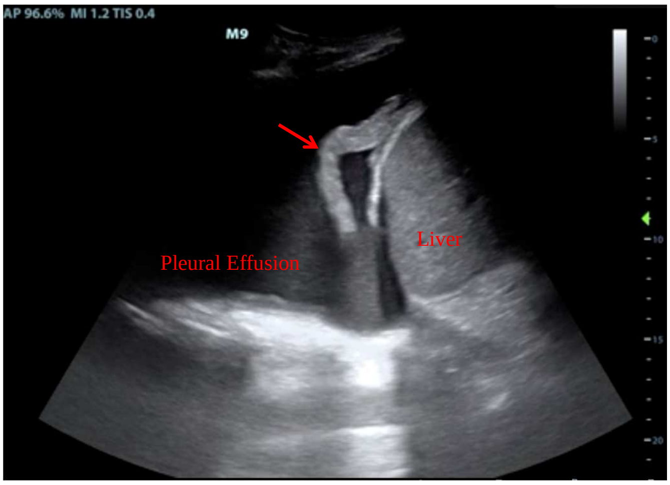
HARVARD MEDICAL SCHOOL

Pleural Effusion


AP 96.6% MI 1.2 TIS 0.4
M9
Pleural Effusion
Liver
0
5
10
15
20

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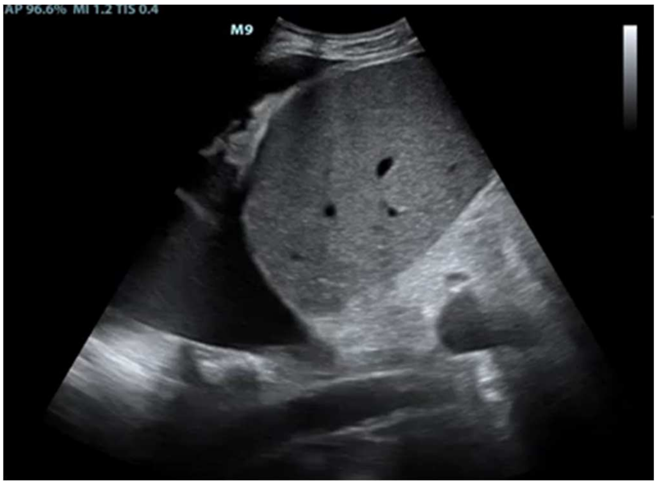
HARVARD MEDICAL SCHOOL

Pleural Effusion


AP 96.6% MI 1.2 TIS 0.4
M9

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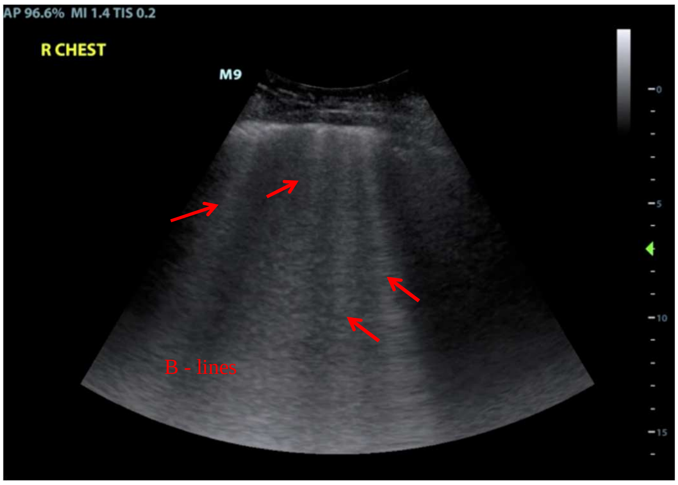
HARVARD MEDICAL SCHOOL

Interstitial Edema


AP 96.6% MI 1.4 TIS 0.2
R CHEST
M9
B - lines
0
5
10
15

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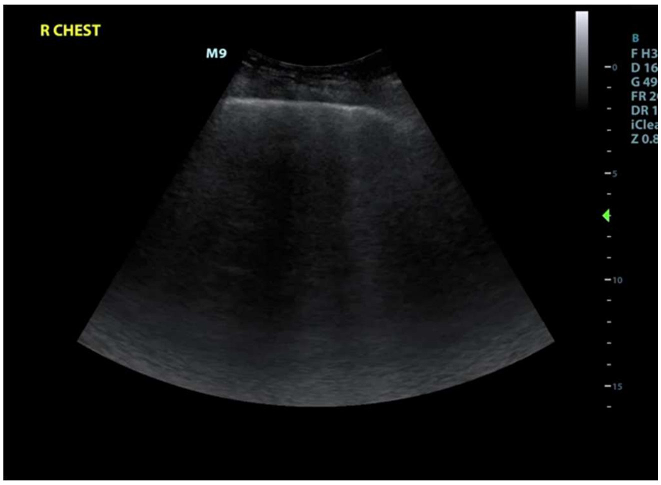
HARVARD MEDICAL SCHOOL

B-lines


R CHEST
M9
B
F H3
D 16
G 49
FR 2
DR 1
iClea
Z 0.8
0
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10
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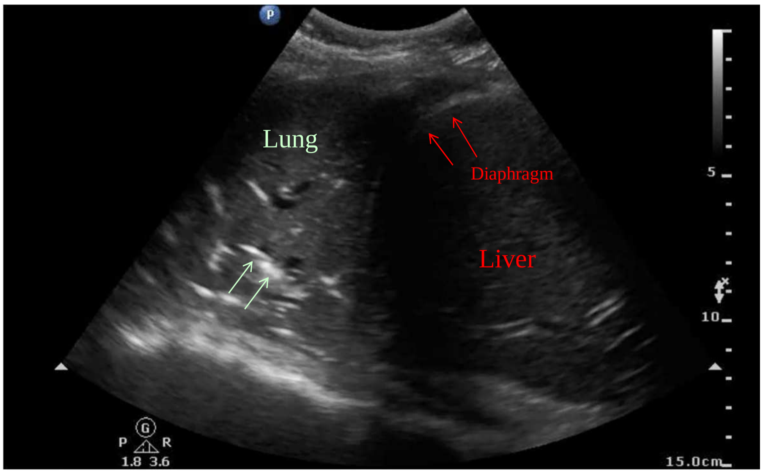
HARVARD MEDICAL SCHOOL

Consolidation


P
Lung
Diaphragm
Liver
5
10
G
P R
1.8 3.6
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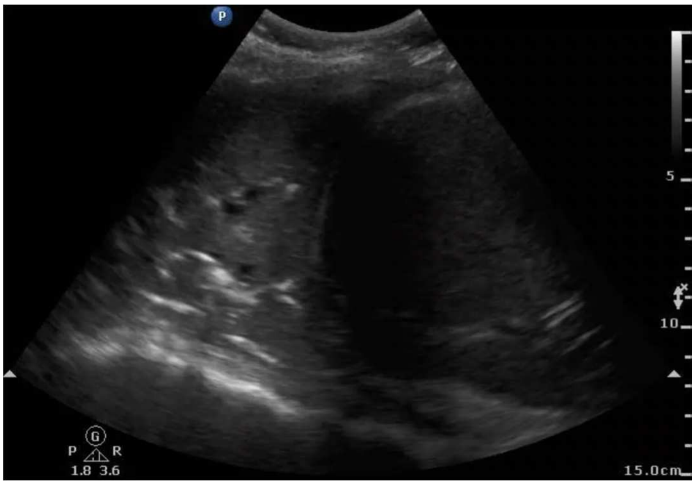
HARVARD MEDICAL SCHOOL

Consolidation


P
5
10
G
P R
1.8 3.6
15.0cm

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HARVARD MEDICAL SCHOOL

Vascular Ultrasound

- Identify venous thrombosis
- Procedures

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HARVARD MEDICAL SCHOOL

DVT exam

- 2-D compression exam
  - Examine vein for echogenic material within lumen
  - Compress vein
    - Vein should fully compress
  - Perform at 5 zones
    - Common FV
    - Common FV at branching of saphenous vein
    - Common FV at bifurcation to deep femoral and superficial femoral vein
    - Proximal superficial femoral vein
    - Popliteal vein

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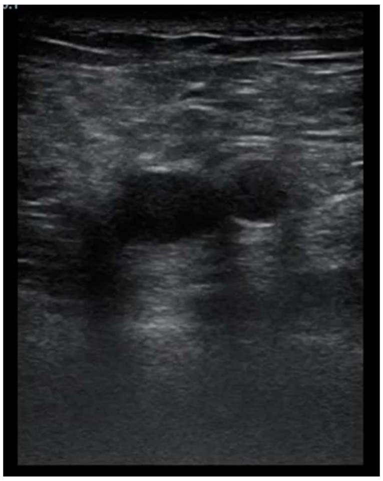
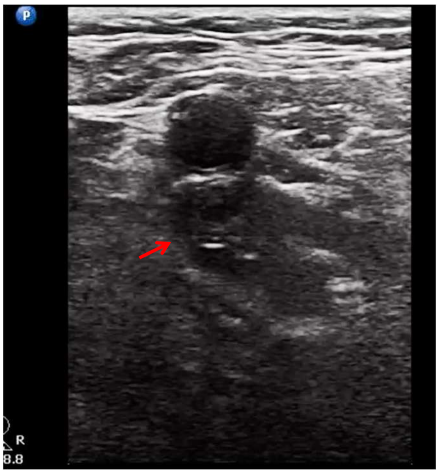
Normal



+ DVT

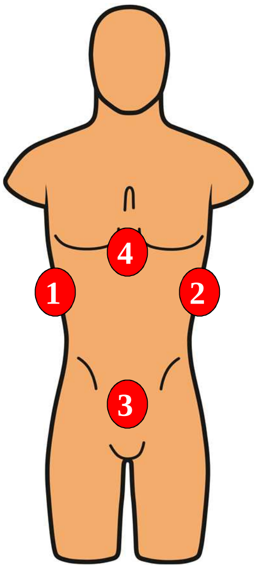


Abdominal Ultrasound

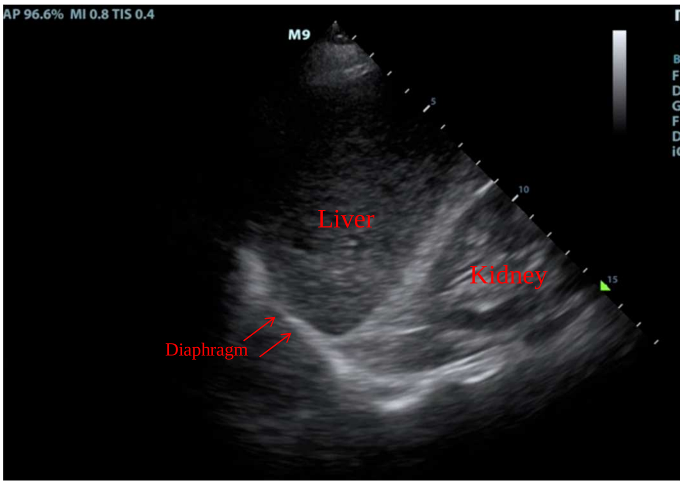
- Identify free fluid in the abdomen
- Identify obstructive nephropathy (hydronephrosis)
- Evaluate abdominal aorta

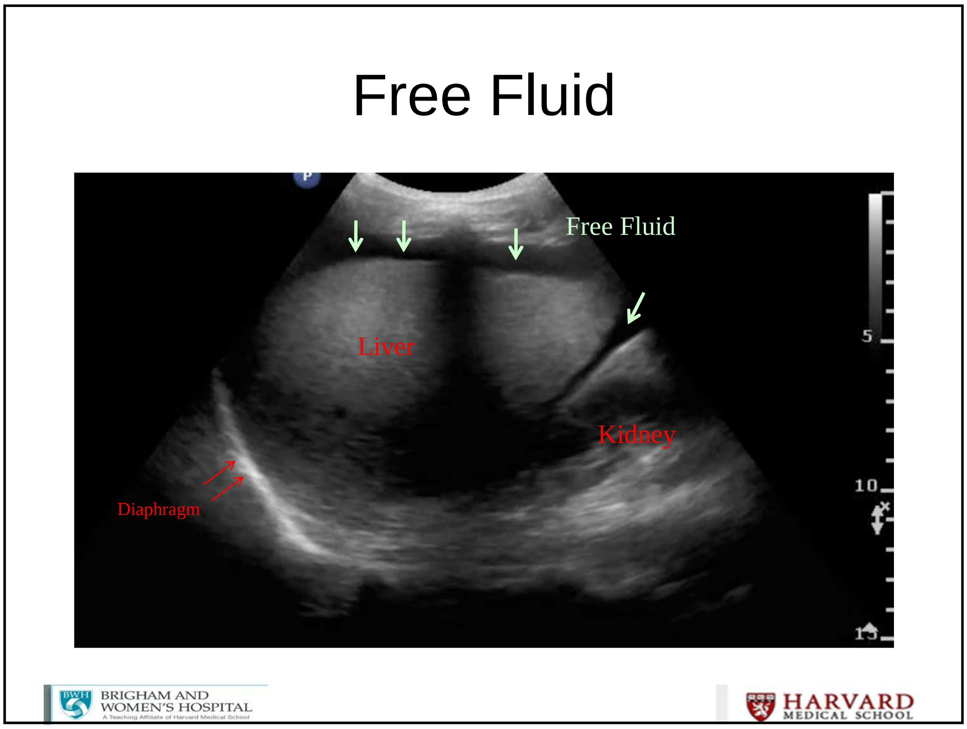
FAST

- *Focused Assessment with Sonography in Trauma* (FAST)
- 4 views
  ① RUQ (Morrison's pouch)
  ② LUQ (splenorenal recess)
  ③ Suprapubic
  ④ Subcostal long-axis
- Rapidly identify free intraperitoneal or pericardial fluid in trauma
- Sensitivity 70 – 95%, specificity 95 – 100%



Normal RUQ


AP 96.6% MI 0.8 TIS 0.4
M9
5
10
15
Liver
Kidney
Diaphragm



Free Fluid

Free Fluid
Liver
Kidney
Diaphragm
5
10
15

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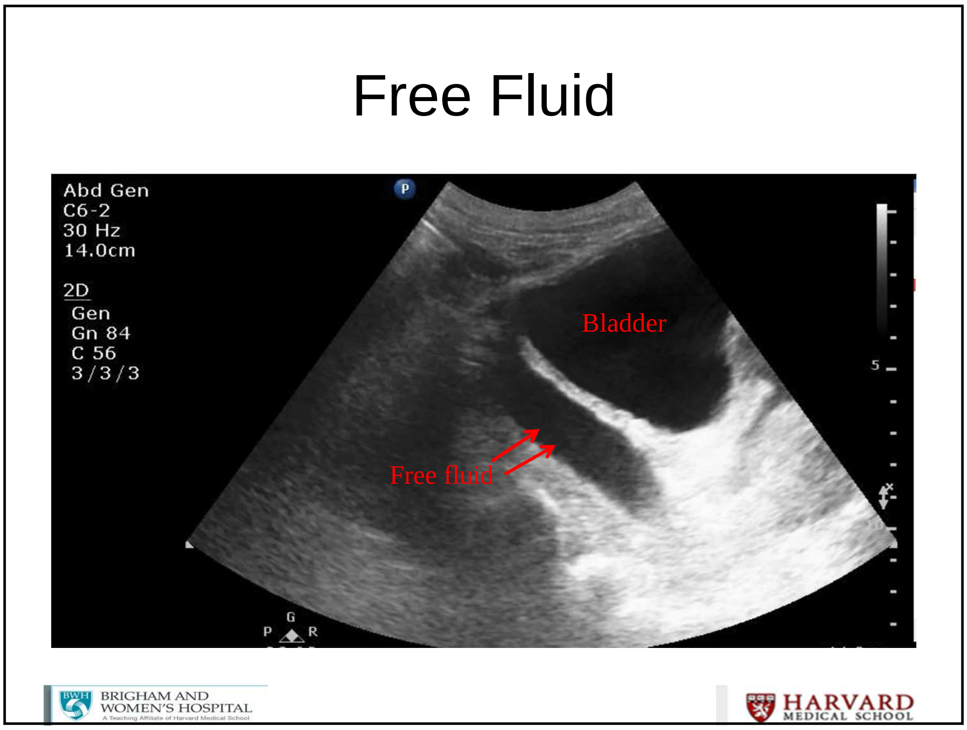
HARVARD MEDICAL SCHOOL



Free Fluid

Abd Gen
C6-2
30 Hz
14.0cm
2D
Gen
Gn 84
C 56
3/3/3
Bladder
Free fluid
P
G
R
5

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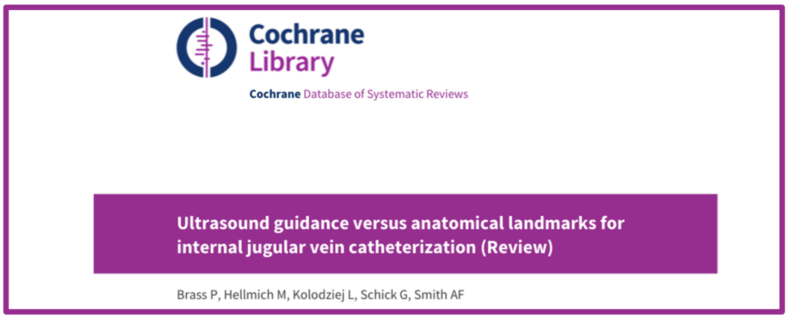
HARVARD MEDICAL SCHOOL

Procedures

- Central line
- Arterial line
- Thoracentesis
- Paracentesis
- Lumbar puncture



Cochrane Library

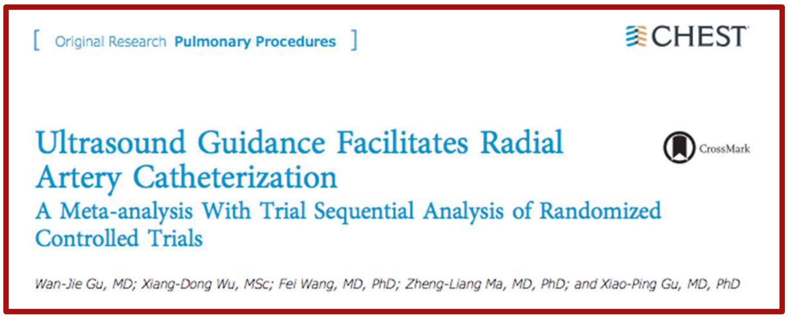
Cochrane Database of Systematic Reviews

Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization (Review)

Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF

- Lower failure rate
- Higher first attempt success rate
- Reduced time to perform procedure
- Decreased arterial punctures
- Decreased rate of hematoma

Cochrane Database Syst Rev. 2015 Jan 9;1:CD006962



[Original Research **Pulmonary Procedures**]

CHEST

Ultrasound Guidance Facilitates Radial Artery Catheterization

A Meta-analysis With Trial Sequential Analysis of Randomized Controlled Trials

CrossMark

Wan-Jie Gu, MD; Xiang-Dong Wu, MSc; Fei Wang, MD, PhD; Zheng-Liang Ma, MD, PhD; and Xiao-Ping Gu, MD, PhD

- Decreases first-attempt failure
- Decreases mean attempts to success
- Decreases mean time to success
- Decreases occurrence of hematoma complications

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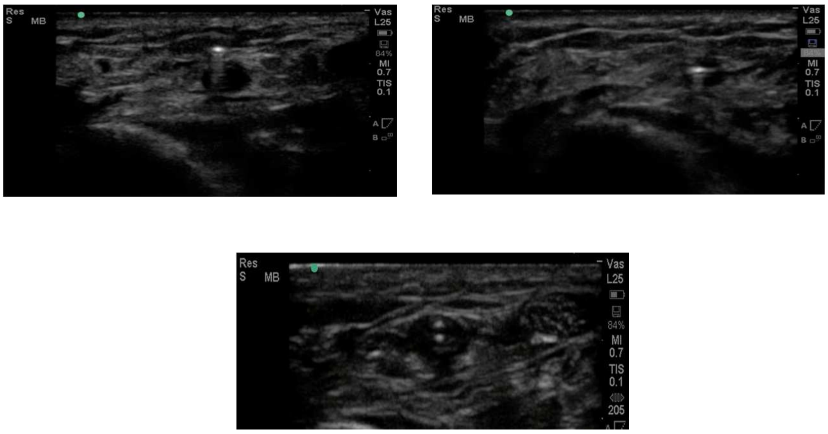
CHEST 2016; 149(1):166-179

HARVARD MEDICAL SCHOOL

Arterial line



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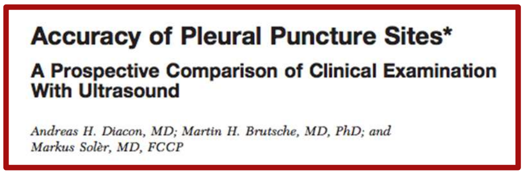
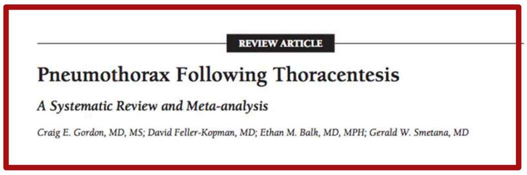


Accuracy of Pleural Puncture Sites*

A Prospective Comparison of Clinical Examination With Ultrasound

Andreas H. Diacon, MD; Martin H. Brutsche, MD, PhD; and Markus Solèr, MD, FCCP



REVIEW ARTICLE

Pneumothorax Following Thoracentesis

A Systematic Review and Meta-analysis

Craig E. Gordon, MD, MS; David Feller-Kopman, MD; Ethan M. Balk, MD, MPH; Gerald W. Smetana, MD

- US increases the yield of thoracentesis and potentially reduces complication rate
- US use was associated with significantly lower risk of pneumothorax (odds ratio [OR], 0.3; 95% CI, 0.2-0.7)

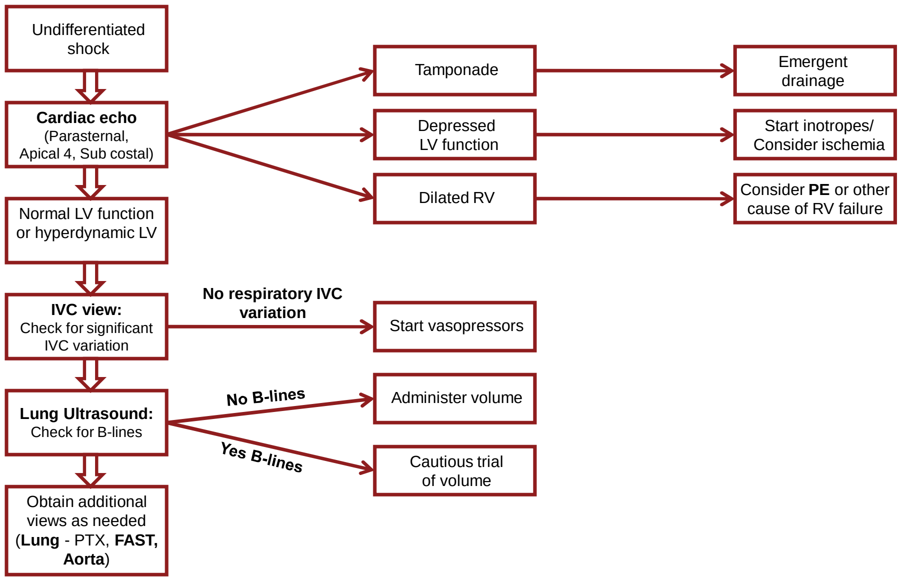
Chest. 2003 Feb;123(2):436-41

Arch Intern Med. 2010;170(4):332-339

Putting all together

ULTRA
SOUND

Shock


Undifferentiated shock

Cardiac echo (Parasternal, Apical 4, Sub costal)

Tamponade → Emergent drainage

Depressed LV function → Start inotropes/ Consider ischemia

Dilated RV → Consider **PE** or other cause of RV failure

Normal LV function or hyperdynamic LV

IVC view: Check for significant IVC variation

No respiratory IVC variation → Start vasopressors

Lung Ultrasound: Check for B-lines

No B-lines → Administer volume

Yes B-lines → Cautious trial of volume

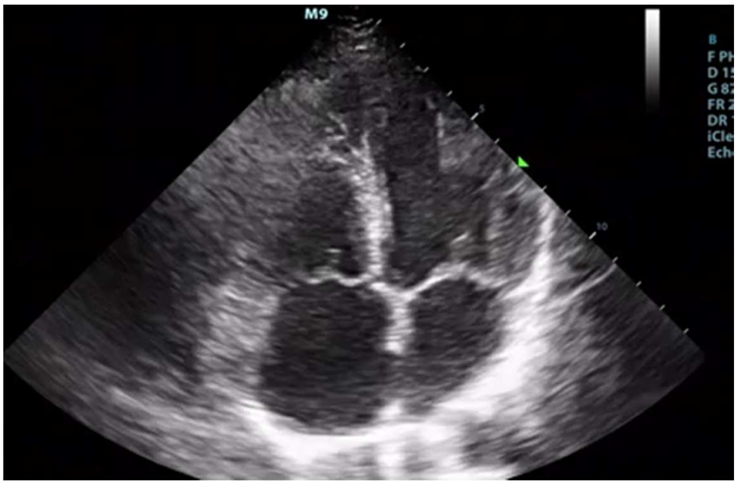
Obtain additional views as needed (**Lung** - PTX, **FAST, Aorta**)

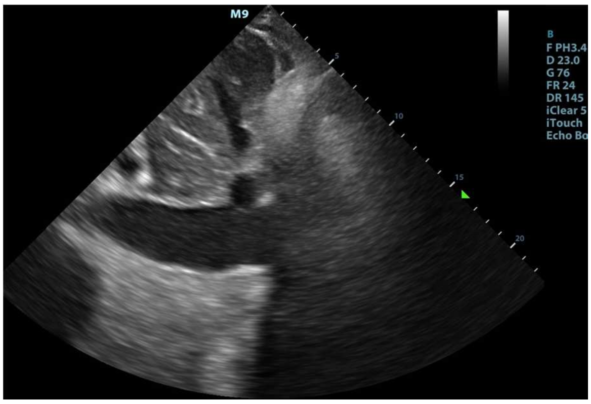
SUMMARY

- Ultrasound can be very useful in the ICU!
- The intensivist should be familiar with the following ultrasound applications: basic cardiac, thoracic, abdominal, vascular, and procedural
- Can help answer critical questions:
  - Why is my patient in shock?
  - Is my patient likely to be fluid responsive?
  - Why is my patient's respiratory status deteriorating?
- Ultrasound has been shown to make common ICU procedures easier and safer

Question # 1

- 40 yo female history of lupus and recent flu like illness admitted to the ICU for fever, hypoxia, and hypotension. Portable CXR is read as right sided effusion. The ED physician administered 4L NS, broad spectrum antibiotics, placed a right subclavian central line, and started the patient on a moderate dose of norepinephrine infusion. Upon arrival to the ICU the patient becomes hypotensive.
- Vitals are as follows: HR 122, BP 81/46, T100.6, RR 28, 93% on 6L NC.
- The nurse asks you want you want to do about the low BP.




M9
5
10
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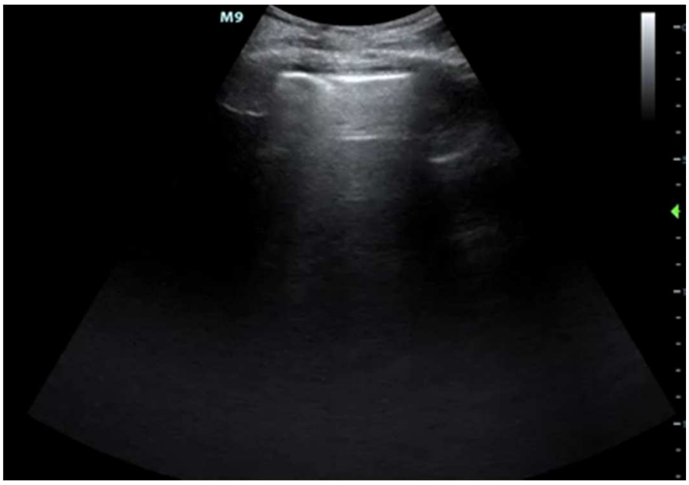
B
F PH3.4
D 23.0
G 76
FR 24
DR 145
iClear 5
iTouch
Echo Bo


M9

What should you do next?

- A. Administer 1 L NS bolus
- B. Administer thrombolytics
- C. Start vasopressin 0.04 U/min
- D. Administer furosemide 100 mg IV push
- E. Needle decompression, followed by chest tube placement

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Answer, Question # 1

- A. Administer 1 L NS bolus
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Question # 2

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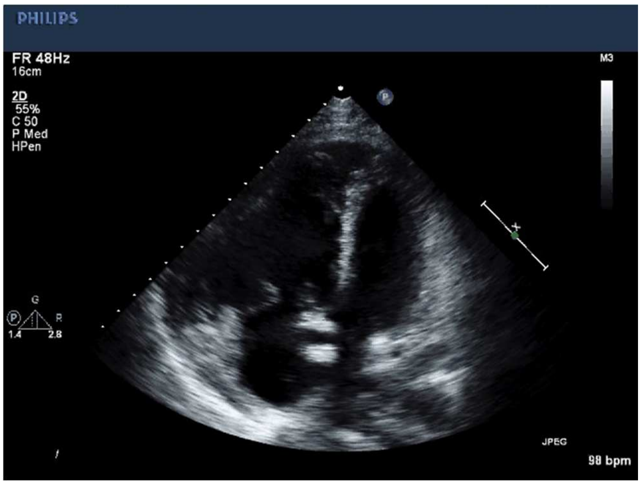

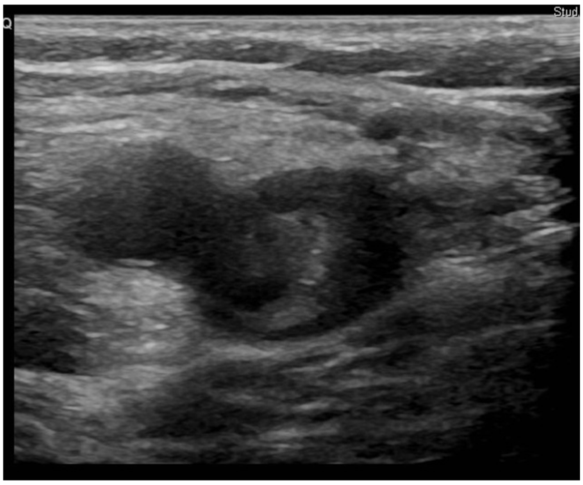

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- E. Needle decompression, followed by chest tube placement

Answer, Question # 2

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- C. Start vasopressin 0.04 U/min
- D. Administer furosemide 100 mg IV push
- E. Needle decompression, followed by chest tube placement

Question # 3

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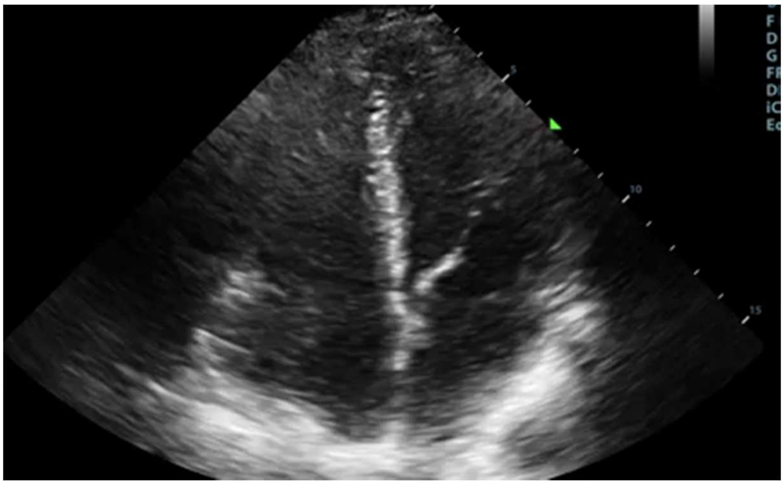
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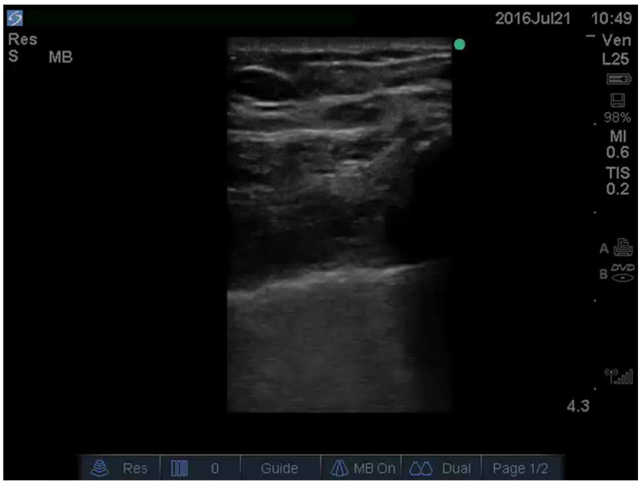
2016Jul21 10:49
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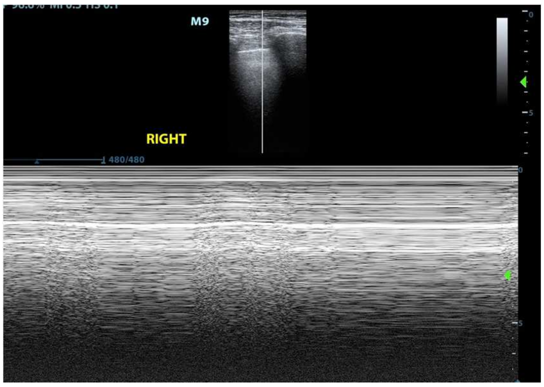
Page 1/2



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- C. Start vasopressin 0.04 U/min
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- E. Needle decompression, followed by chest tube placement

References

- Frankel HL, et al. Crit Care Med. 2015 Nov;43(11):2479-502.
- Levitov A, et al. Crit Care Med. 2016 Jun;44(6):1206-27
- Lichtenstein DA, et al.Chest. 2008 Jul;134(1):117-25.
- Cardenas-Garcia J et al. Crit Care Clin. 2015 Jan;31(1):43-66.

Post-Intensive Care Syndrome

or

What does it mean to be okay?

Daniela J. Lamas, MD
Pulmonary and Critical Care Medicine /Brigham and Women's Hospital
Instructor/Harvard Medical School

Disclosures

- I have no relevant disclosures

Outline

- Epidemiology
- Post-intensive care syndrome (PICS)
- PICS – Family
- Treatment?
- Research and Clinical Efforts

Take Home Messages

- We are saving lives
- Things we do in the ICU have long term consequences
- The standard solutions might not work here – we will need to be creative to solve these problems

Outline

- **Epidemiology**
- Post-intensive care syndrome (PICS)
- PICS – Family
- Treatment?
- Research and Clinical Efforts

How many ICU survivors are there?

- >70,000 adults cared for in ICUs every day in the US
- About 5.7 million ICU admissions per year
- 4.8 million survive
- > 1% GDP
- What happens to them?

Anecdotal Evidence – From Doctors

- Young man with ARDS, ECMO for weeks
- Episodes of septic shock, MSOF
- Months long ventilator weaning

- But, excellent recovery
- No evidence of cognitive impairment

- "Should have been content… but wasn't"

Schelling, G *Chest* 2013

Anecdotal Evidence – "The Imaginary War"

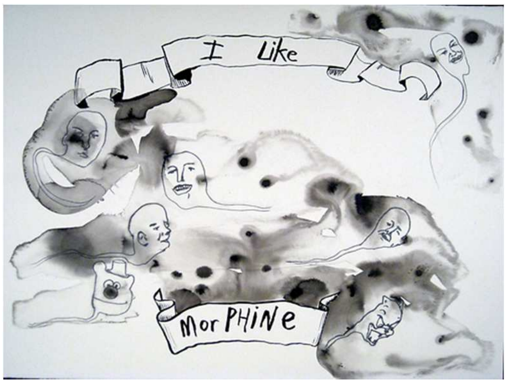
- Tense, withdrawn, anxious

- Finally asked: "Is the war over?"

- Family was killed
- He had been hogtied, naked and cold, tortured
- Nightmares and flashbacks
- Veteran of an imaginary war

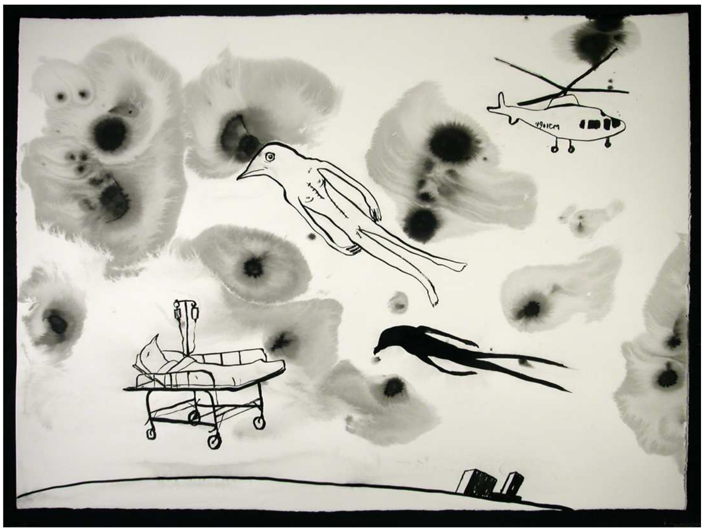
Schelling, G *Chest* 2013

Anecdotal Evidence – Patients



- Nancy Andrews
- TEDx talk
- Memories of things ***that never happened***

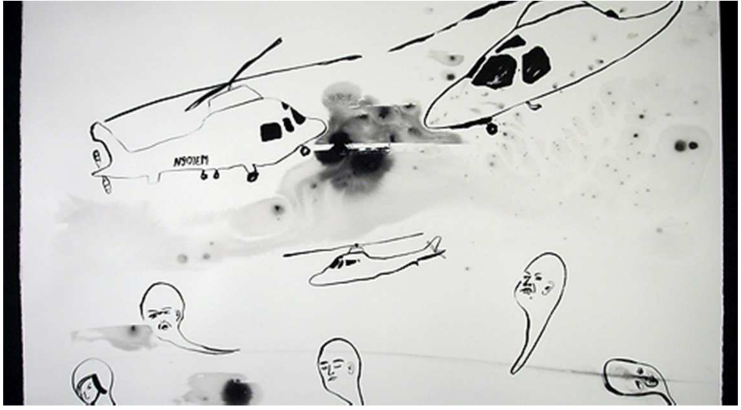
Nancyandrews.net



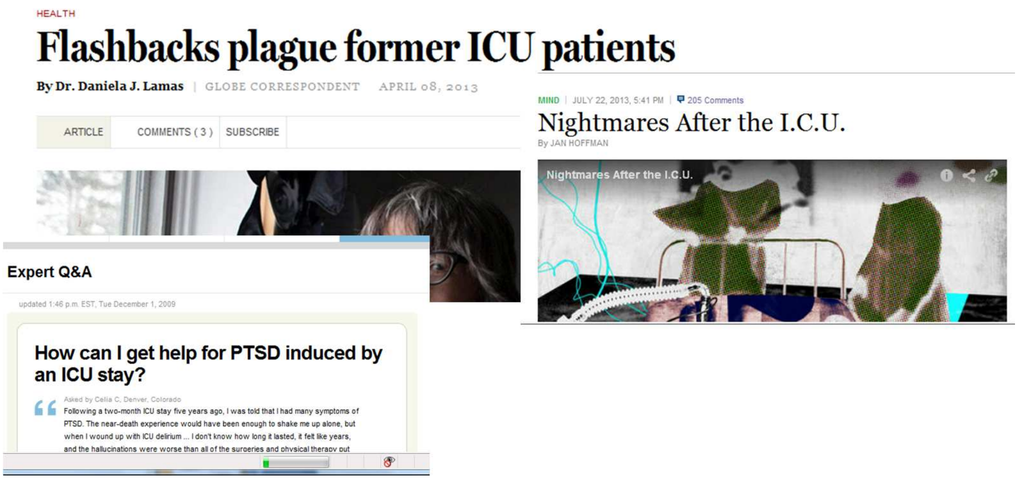
"For 3 weeks I was held in a room, I was tied to the bed if I tried to get away. I couldn't talk; I couldn't eat; I was not allowed to sleep; Groups of people would enter the room and look at me and talk about me and I was sometimes undressed in front of a small audience. I was shot full of drugs; I was too weak to move; I could not see my body but it had been cut nearly in half. Insects crawled on the walls and ceiling. "

Nancyandrews.net

"Where was I? They asked me everyday and I never knew the answer. I was in the ICU of one of the best hospitals in the world, where nurses and doctors were using all the most current medical know-how to save my life. In reality, the ICU is a torture chamber. **If you take away the knowledge that everyone is trying to keep you alive, what is actually happening can be pretty dreadful.** Being on a ventilator is a nightmare, and your ability to communicate by speaking is taken away. If you are agitated you will be restrained so that you stay in bed and don't hurt or kill yourself. "



Anecdotal Evidence – Lay press



HEALTH

Flashbacks plague former ICU patients

By Dr. Daniela J. Lamas | GLOBE CORRESPONDENT APRIL 08, 2013

MIND | JULY 22, 2013, 5:41 PM | 205 Comments

Nightmares After the I.C.U.

By JAN HOFFMAN

Expert Q&A

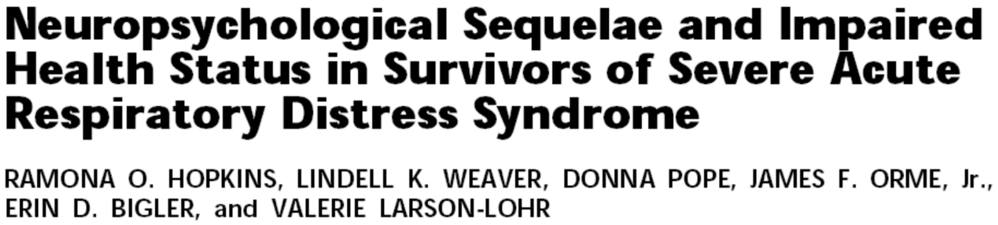
updated 1:46 p.m. EST, Tue December 1, 2009

How can I get help for PTSD induced by an ICU stay?

Asked by Celia C, Denver, Colorado

Following a two-month ICU stay five years ago, I was told that I had many symptoms of PTSD. The near-death experience would have been enough to shake me up alone, but when I wound up with ICU delirium ... I don't know how long it lasted, it felt like years, and the hallucinations were worse than all of the surgeries and physical therapy put

More than Anecdotal Evidence



Neuropsychological Sequelae and Impaired Health Status in Survivors of Severe Acute Respiratory Distress Syndrome

RAMONA O. HOPKINS, LINDELL K. WEAVER, DONNA POPE, JAMES F. ORME, Jr., ERIN D. BIGLER, and VALERIE LARSON-LOHR

- Emphasized that lung function could return to near normal
- Survivors instead limited by weakness, and cognitive dysfunction
- Alive **≠ alive and well**

AJRCCM 1999

- One year after onset of ARDS, we found that:
  - 78% of ARDS survivors demonstrated impaired cognitive function including impaired memory, attention, and concentration;
  - 48% had decreased mental processing speed; and
  - 30% had global cognitive decline.

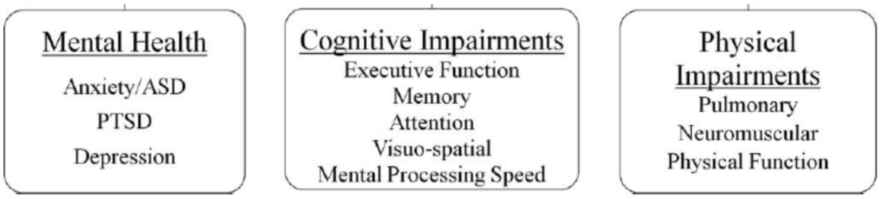
For example, at this level of dysfunction ARDS patients reported that they had problems remembering appointments, what to buy at the grocery store, what people say to them, and if they took their medications. ARDS survivors reported difficulty remembering and following directions, especially if there were more than 2 or 3 items to be remembered. Several survivors reported that if distracted while cooking, they forgot that they had something on the stove, until the food was smoking and burning.

Outline

- Epidemiology
- **Post-intensive care syndrome (PICS)**
- PICS – Family
- Treatment?
- Research and Clinical Efforts

Post-Intensive Care Syndrome

- "Awareness would be improved by use of a single term"
- New or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization



Mental Health
Anxiety/ASD
PTSD
Depression

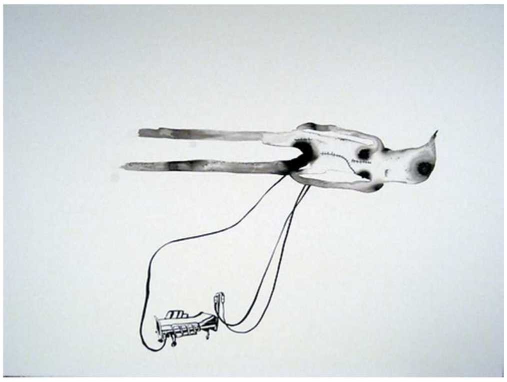
Cognitive Impairments
Executive Function
Memory
Attention
Visuo-spatial
Mental Processing Speed

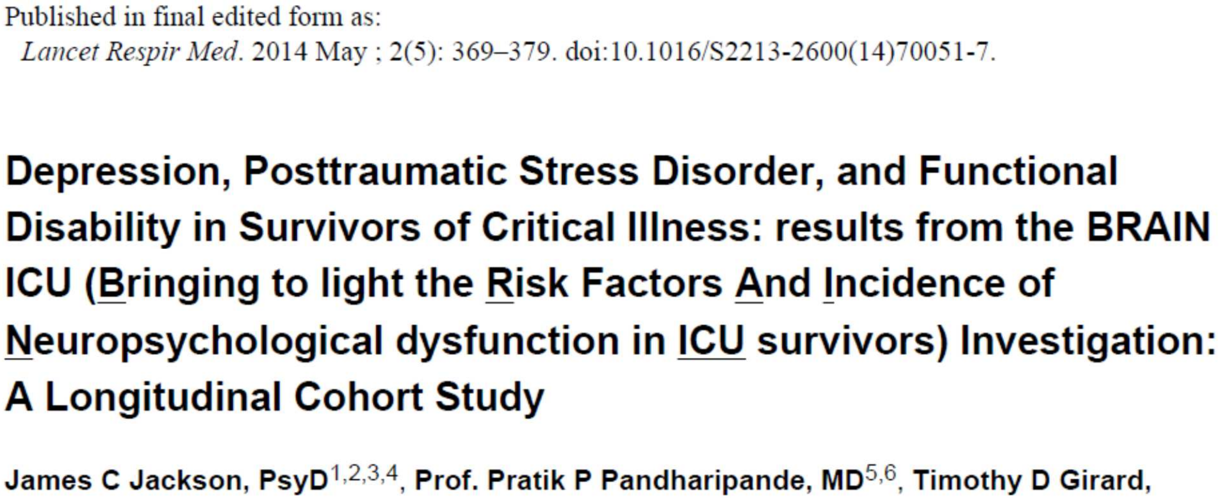
Physical Impairments
Pulmonary
Neuromuscular
Physical Function

Needham DM *Crit Care Med* 2012

Mental Health

- Anxiety
- Depression
- Post-traumatic stress disorder





Published in final edited form as:
Lancet Respir Med. 2014 May ; 2(5): 369–379. doi:10.1016/S2213-2600(14)70051-7.

Depression, Posttraumatic Stress Disorder, and Functional Disability in Survivors of Critical Illness: results from the BRAIN ICU (Bringing to light the Risk Factors And Incidence of Neuropsychological dysfunction in ICU survivors) Investigation: A Longitudinal Cohort Study

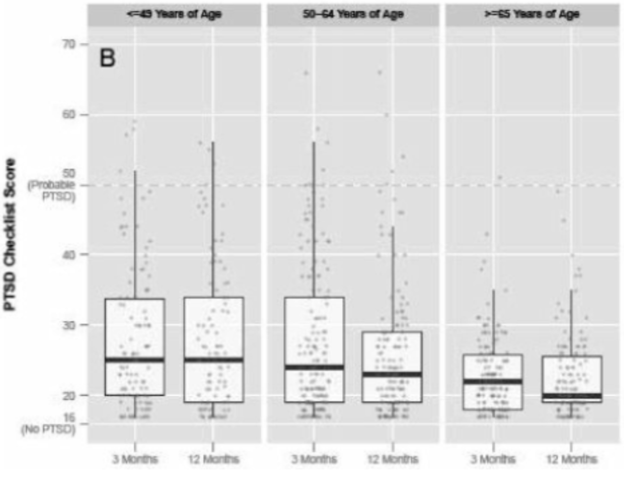
James C Jackson, PsyD[1,2,3,4], Prof. Pratik P Pandharipande, MD[5,6], Timothy D Girard,

www.icudelirium .org

Brain ICU cohort

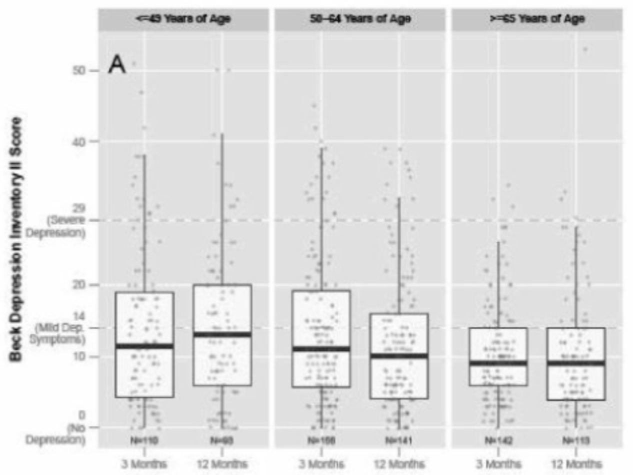
- Adults admitted to medical/surgical ICUs with respiratory failure, cardiogenic shock, or septic shock.
- **Excluded** individuals mechanically ventilated at any time two months before the current ICU admission, spent >5 days in an ICU during the month before the current ICU admission, or spent >72 hours with organ dysfunction in the current ICU admission
- And individuals with significant preexisting cognitive impairment identified
- And individuals at high risk for preexisting cognitive deficits due to neurodegenerative dz, recent cardiac surgery or suspected anoxic injury
- **821 patients enrolled, then evaluated at 3 and 12 months**

7% of survivors have PTSD

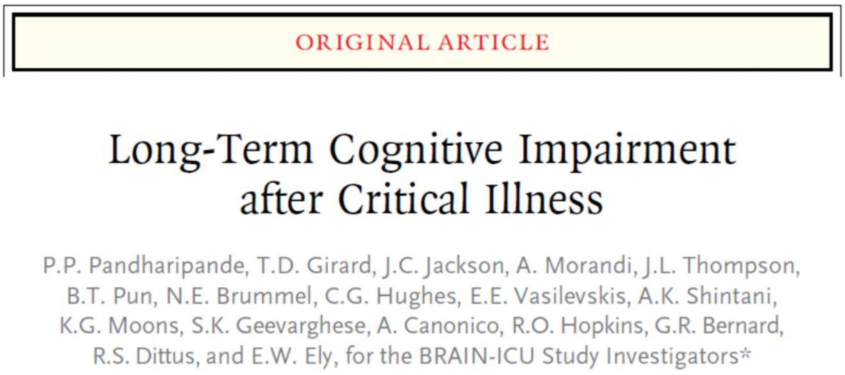


Patel AJRCCM 2016

But 33% have depression



Cognitive Impairments



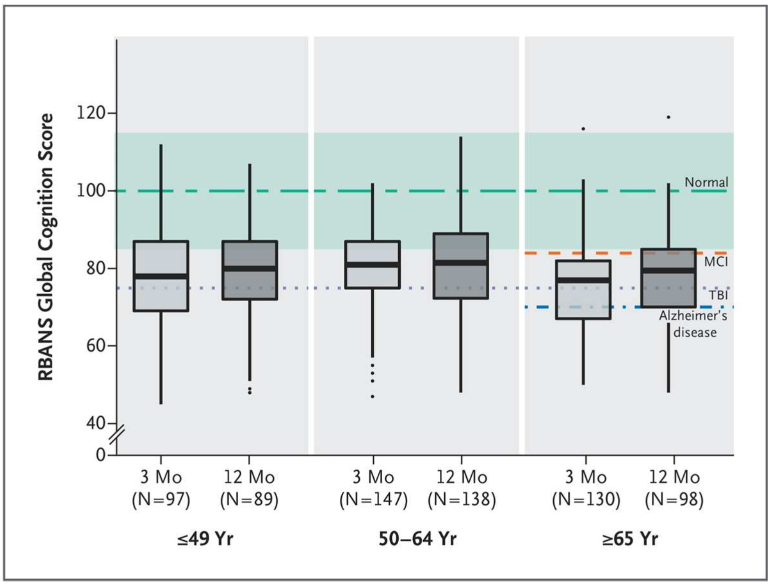
ORIGINAL ARTICLE

Long-Term Cognitive Impairment after Critical Illness

P.P. Pandharipande, T.D. Girard, J.C. Jackson, A. Morandi, J.L. Thompson, B.T. Pun, N.E. Brummel, C.G. Hughes, E.E. Vasilevskis, A.K. Shintani, K.G. Moons, S.K. Geevarghese, A. Canonico, R.O. Hopkins, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the BRAIN-ICU Study Investigators*

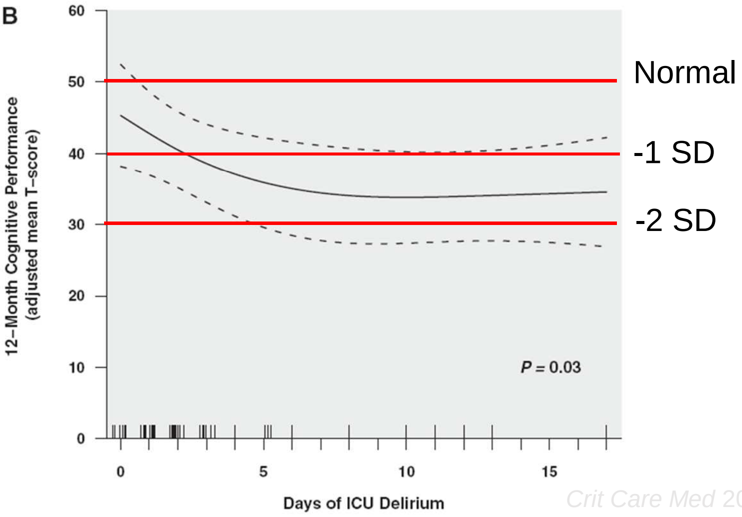
NEJM 2013

Global Cognition Scores in Survivors of Critical Illness.



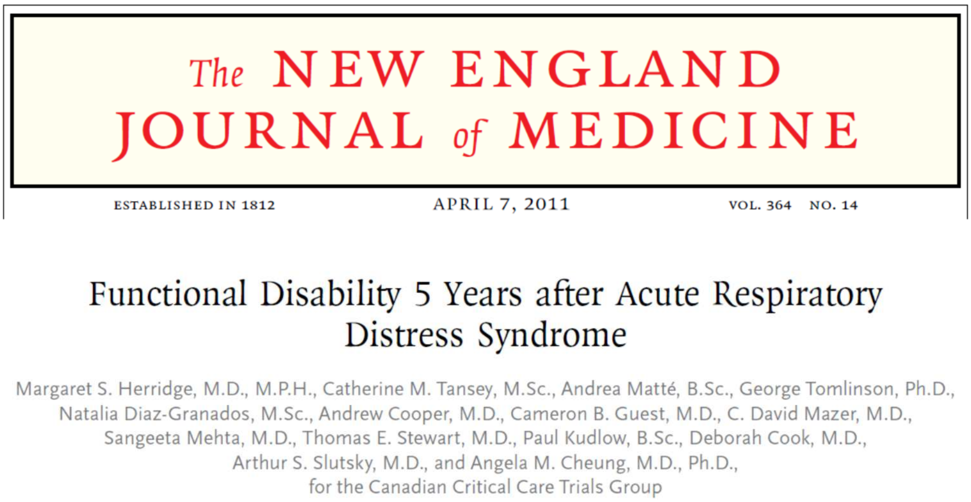
Delirium as a predictor of long-term cognitive impairment in survivors of critical illness

Timothy D. Girard, MD, MSCI; James C. Jackson, PsyD; Pratik P. Pandharipande, MD, MSCI; Brenda T. Pun, MSN; Jennifer L. Thompson, MPH; Ayumi K. Shintani, PhD, MPH; Sharon M. Gordon, PsyD; Angelo E. Canonico, MD; Robert S. Dittus, MD, MPH; Gordon R. Bernard, MD; E. Wesley Ely, MD, MPH



Crit Care Med 2010

Physical Impairments



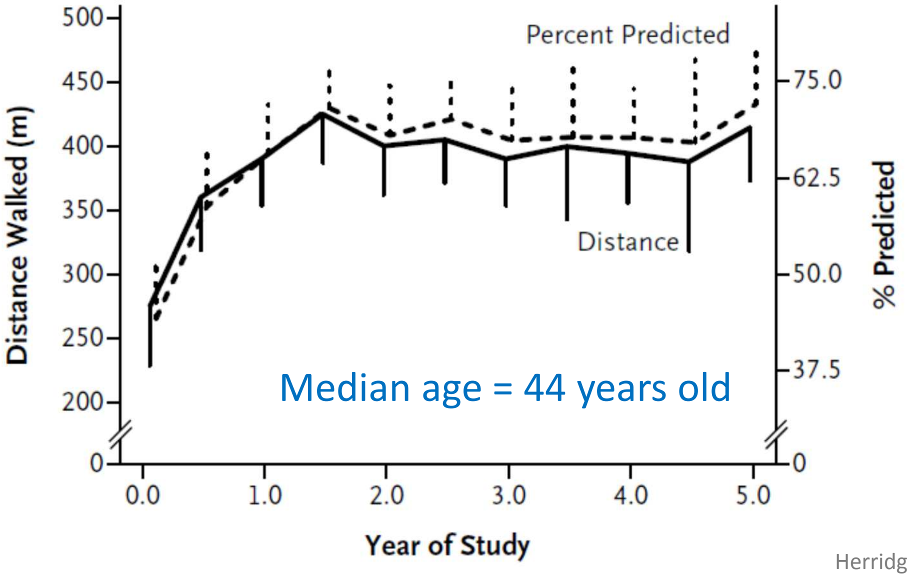
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2011 VOL. 364 NO. 14

Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D.,
Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D.,
Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D.,
Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D.,
for the Canadian Critical Care Trials Group

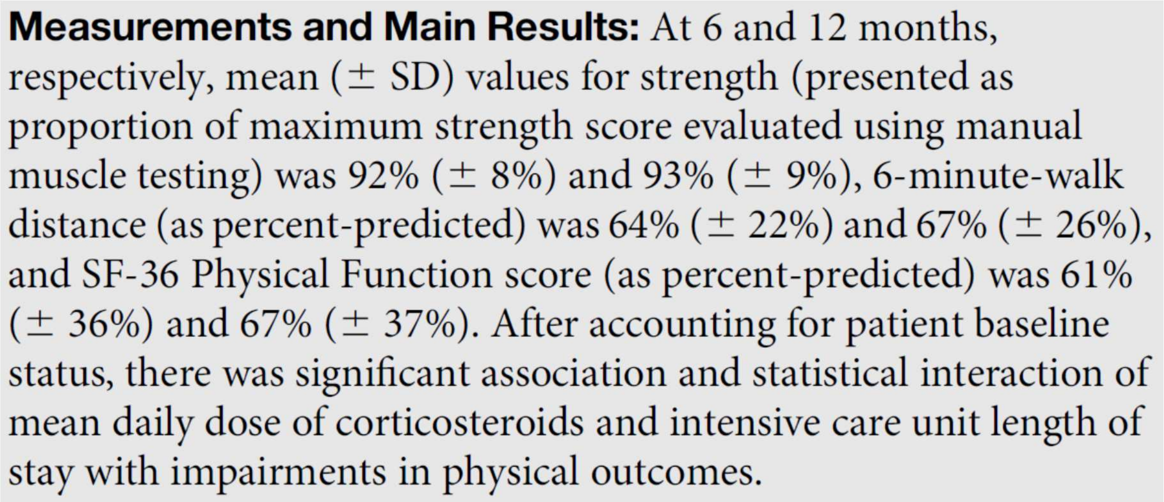
Physical impairments are long lasting



Median age = 44 years old

Herridge *NEJM* 2011

Physical Impairments – Risk Factors



Measurements and Main Results: At 6 and 12 months, respectively, mean (± SD) values for strength (presented as proportion of maximum strength score evaluated using manual muscle testing) was 92% (± 8%) and 93% (± 9%), 6-minute-walk distance (as percent-predicted) was 64% (± 22%) and 67% (± 26%), and SF-36 Physical Function score (as percent-predicted) was 61% (± 36%) and 67% (± 37%). After accounting for patient baseline status, there was significant association and statistical interaction of mean daily dose of corticosteroids and intensive care unit length of stay with impairments in physical outcomes.

Needham AJRCCM 2014

Post-Intensive Care Syndrome

- New or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization

What do you tell patients when they leave the ICU?

What do you tell their families?

Needham DM *Crit Care Med* 2012

A case of a 51 year old woman…

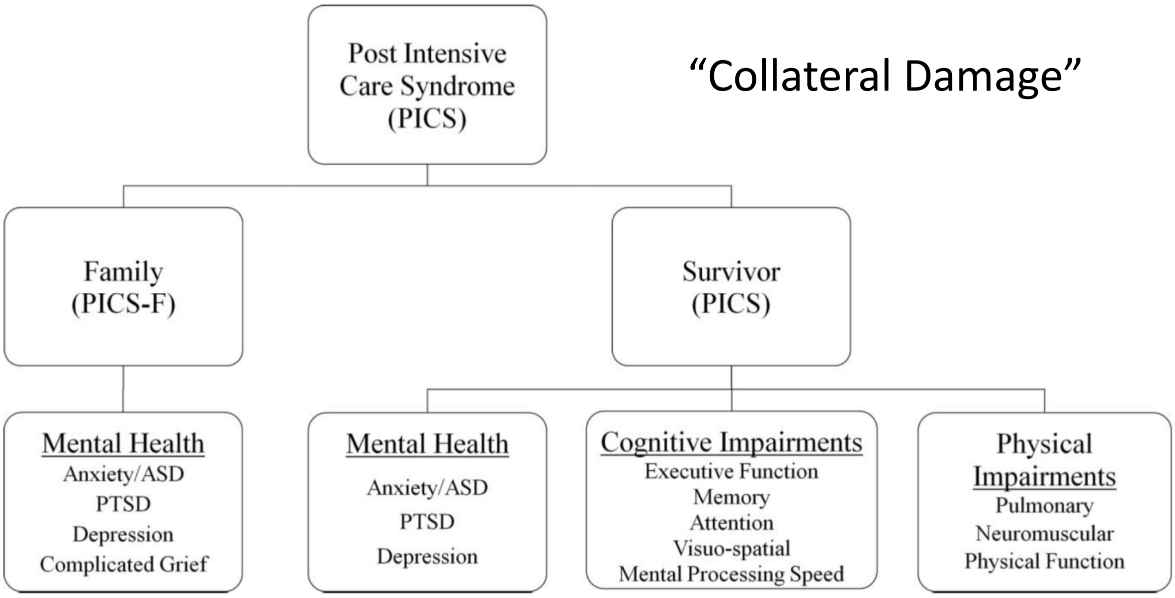
- H1N1 influenza
- ARDS, AKI, Shock
- Ventilated, ECMO x 8 days, CRRT, multiple pressors
- Trached, delirious
- ~8 weeks in the ICU

A case…

- Now, three years later, she's back to her prior quality of life
- Maybe better?
- Newly married, moved to St. Croix
- Remembers little of her ICU stay, does remember anxiety and frustration at rehab

But her brother describes anxiety and ? PTSD

"Collateral Damage"



Post Intensive Care Syndrome (PICS)

Family (PICS-F)

Survivor (PICS)

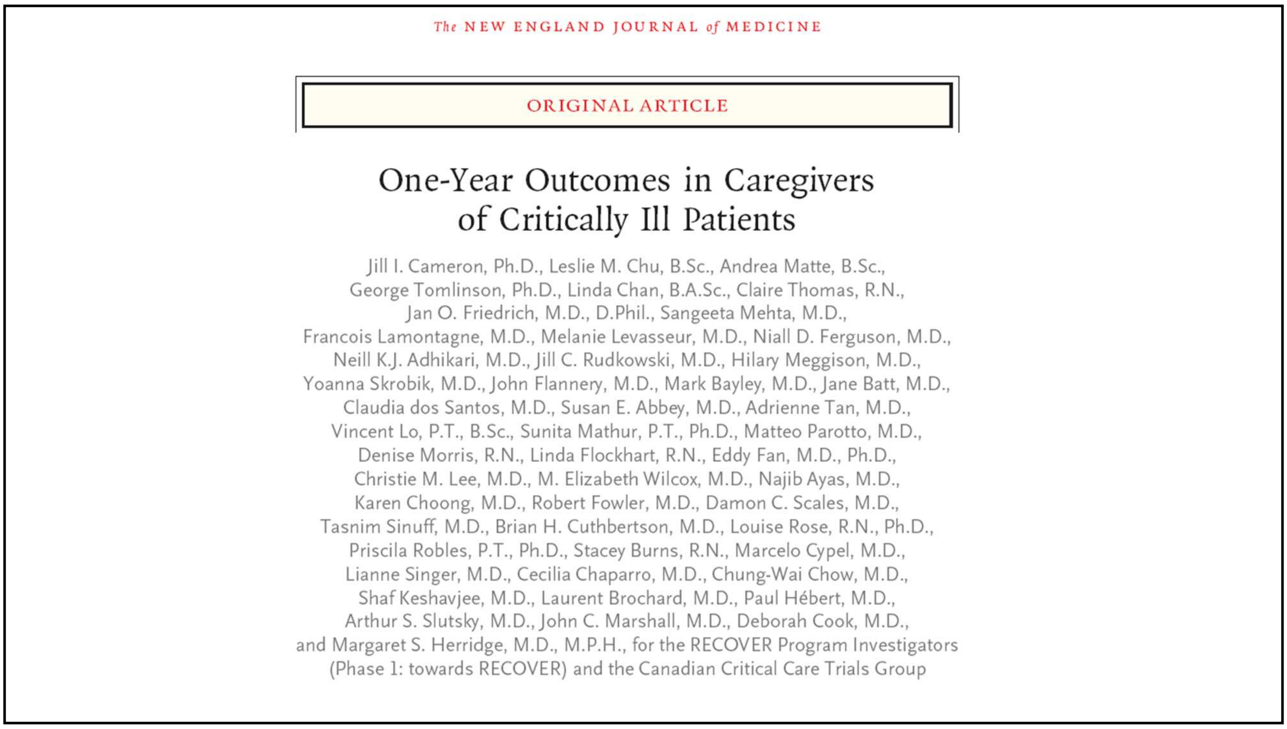
Mental Health
Anxiety/ASD
PTSD
Depression
Complicated Grief

Mental Health
Anxiety/ASD
PTSD
Depression

Cognitive Impairments
Executive Function
Memory
Attention
Visuo-spatial
Mental Processing Speed

Physical Impairments
Pulmonary
Neuromuscular
Physical Function

Needham DM *Crit Care Med* 2012



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

One-Year Outcomes in Caregivers of Critically Ill Patients

Jill I. Cameron, Ph.D., Leslie M. Chu, B.Sc., Andrea Matte, B.Sc.,
George Tomlinson, Ph.D., Linda Chan, B.A.Sc., Claire Thomas, R.N.,
Jan O. Friedrich, M.D., D.Phil., Sangeeta Mehta, M.D.,
Francois Lamontagne, M.D., Melanie Levasseur, M.D., Niall D. Ferguson, M.D.,
Neill K.J. Adhikari, M.D., Jill C. Rudkowski, M.D., Hilary Meggison, M.D.,
Yoanna Skrobik, M.D., John Flannery, M.D., Mark Bayley, M.D., Jane Batt, M.D.,
Claudia dos Santos, M.D., Susan E. Abbey, M.D., Adrienne Tan, M.D.,
Vincent Lo, P.T., B.Sc., Sunita Mathur, P.T., Ph.D., Matteo Parotto, M.D.,
Denise Morris, R.N., Linda Flockhart, R.N., Eddy Fan, M.D., Ph.D.,
Christie M. Lee, M.D., M. Elizabeth Wilcox, M.D., Najib Ayas, M.D.,
Karen Choong, M.D., Robert Fowler, M.D., Damon C. Scales, M.D.,
Tasnim Sinuff, M.D., Brian H. Cuthbertson, M.D., Louise Rose, R.N., Ph.D.,
Priscila Robles, P.T., Ph.D., Stacey Burns, R.N., Marcelo Cypel, M.D.,
Lianne Singer, M.D., Cecilia Chaparro, M.D., Chung-Wai Chow, M.D.,
Shaf Keshavjee, M.D., Laurent Brochard, M.D., Paul Hébert, M.D.,
Arthur S. Slutsky, M.D., John C. Marshall, M.D., Deborah Cook, M.D.,
and Margaret S. Herridge, M.D., M.P.H., for the RECOVER Program Investigators
(Phase 1: towards RECOVER) and the Canadian Critical Care Trials Group

Findings

- Patients mechanically ventilated 7+ days, survived
- Caregivers mean age 53; 70% women; 61% caring for a spouse
- 67% initially and 43% at 1 year reported high levels of depressive symptoms
- Depressive symptoms decreased at least partially with time in 84% of the caregivers but did not in 16%
- Worse mental health outcomes: younger age, greater effect of patient care on other activities, less social support, less sense of control over life, and less personal growth.
  - No patient variables were consistently associated with caregiver outcomes over time.

Outline

- Epidemiology
- Post-intensive care syndrome (PICS)
- PICS – Family
- **Treatment?**
- Research and Clinical Efforts

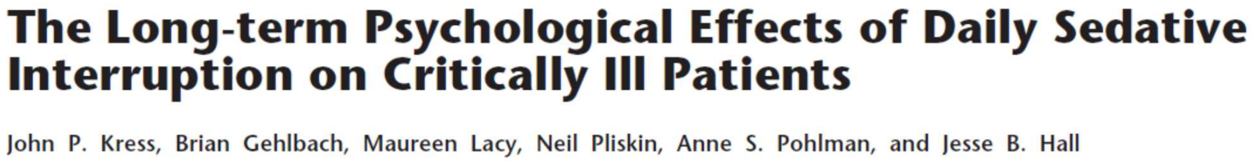
Treatment?

- No studies about interventions for PICS *per se*
- Emphasis should be on **recognition** and **education**
- However, several studies on **prevention**

Prevention is key!

- Decrease ICU length of stay
- Decrease duration of mechanical ventilation
- Decrease delirium

Best practices in the ICU have the potential to reduce PICS



The Long-term Psychological Effects of Daily Sedative Interruption on Critically Ill Patients

John P. Kress, Brian Gehlbach, Maureen Lacy, Neil Pliskin, Anne S. Pohlman, and Jesse B. Hall

- Would interruption of sedation cause psychological distress?
- In fact, evidence for reduction in PTSD

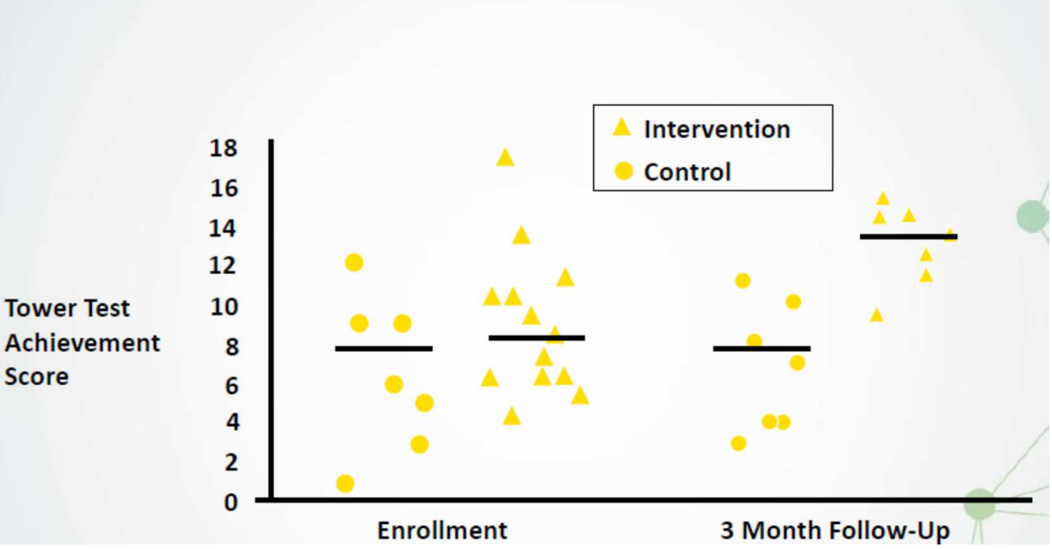
AJRCCM 2003

What about late cognitive/physical rehab

- Pilot, feasibility RCT (8 control, 13 intervention)
- ICU survivors with cognitive or physical impairment at discharge (BRAIN-ICU)
- Intervention: in-home cognitive, physical, function rehab via telemedicine x 3 months
- 6 in-person visits
- 6 televisits
- Outcomes at 3 month

Jackson J, Ely EW et al. Cognitive and Physical Rehabilitation of ICU Survivors: results of the RETURN randomized controlled pilot investigation. Crit Care Med Apr2012; 40 (4): 1088-1097.

Cognitive & Physical Rehabilitation: RETURN



Jackson CCM 2012

ICU Diaries and PTSD

“I started to see this pattern of people with flashbacks and nightmares. They had very little factual memory, but also had these hallucinations, paranoid delusions of nightmares and alien abductions and nurses trying to kill them. That seemed to be the precipitant for PTSD for a portion of the patients — they couldn’t reject these memories.”

- Christina Jones, nurse consultant in UK

ICU Diaries

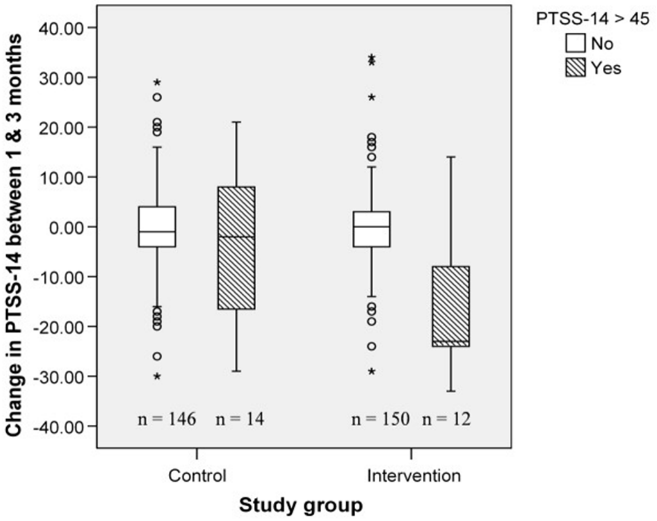
Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial

Christina Jones[1,2], Carl Bäckman[3], Maurizia Capuzzo[4], Ingrid Egerod[5], Hans Flaatten[6], Cristina Granja[7], Christian Rylander[8], Richard D Griffiths[1,2*], the RACHEL group

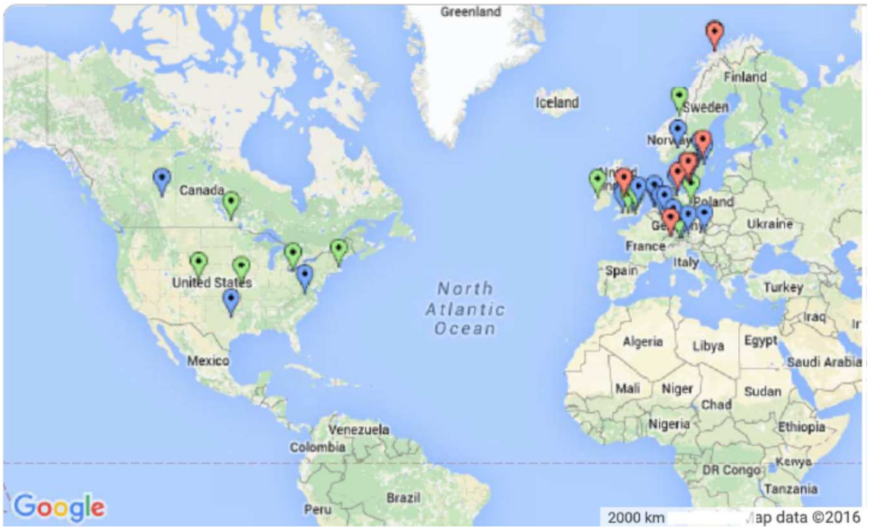
Crit Care 2010

ICU Diaries

- Patients requiring more than 72 hours in ICU
- PTSD assessed at 1 and 3 months
- Diary given out to patients at 1 month (after PTSD assessment)



ICU Diaries: Should everyone do it?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Kenya
Tanzania
Venezuela
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Brazil
Google
2000 km
ap data ©2016

Icu-diary.org

PICS – F: What to do?

- Things we try:
  - Communication via frequent family meetings, open visitation, family members on rounds (observational data)
  - Family participation in bedside care of patients (e.g. applying lip balm, massage)
- No clear data
- Proactive palliative care meetings with families of patients on vent > 7 days, not expected to wean or die in 72 hours did *not* reduce anxiety/depression.

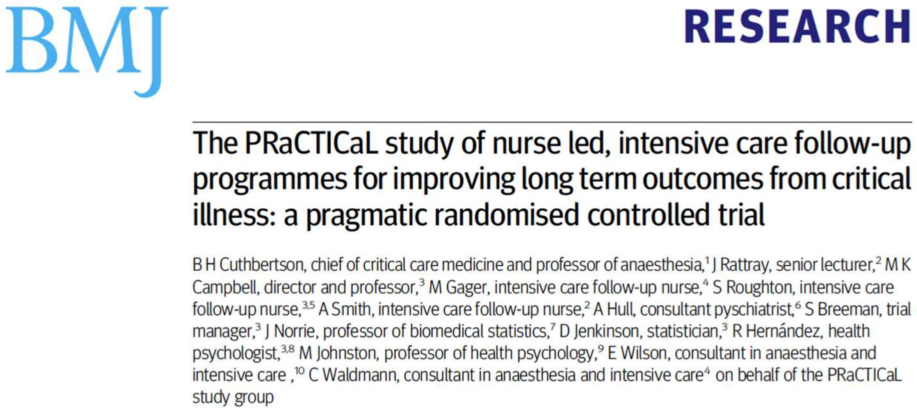
Outline

- Epidemiology
- Post-intensive care syndrome (PICS)
- PICS – Family
- ~~Treatment~~? Prevention
- **Research and Clinical Efforts**

Brigham and Women’s ICU Recovery Clinic

- Screen for mood disorders, PTSD, cognitive dysfunction and insomnia
- Medical follow-up
- Medication Reconciliation
- Communication with PCP

Are they helpful?



BMJ

RESEARCH

The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial

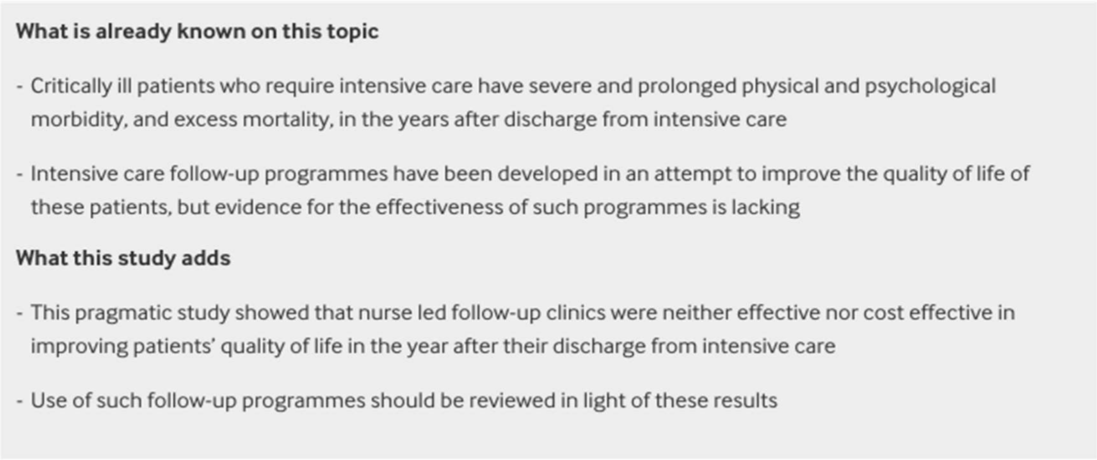
B H Cuthbertson, chief of critical care medicine and professor of anaesthesia,[1] J Rattray, senior lecturer,[2] M K Campbell, director and professor,[3] M Gager, intensive care follow-up nurse,[4] S Roughton, intensive care follow-up nurse,[3,5] A Smith, intensive care follow-up nurse,[2] A Hull, consultant pyschiatrist,[6] S Breeman, trial manager,[3] J Norrie, professor of biomedical statistics,[7] D Jenkinson, statistician,[3] R Hernández, health psychologist,[3,8] M Johnston, professor of health psychology,[9] E Wilson, consultant in anaesthesia and intensive care ,[10] C Waldmann, consultant in anaesthesia and intensive care[4] on behalf of the PRaCTICaL study group

Study plan

- 286 post-ICU patients randomly assigned to nurse-led clinic or standard of care
- Intervention: visits at 3, 9 months with psych screening and physical rehabilitation
- Outcome: HRQOL (SF-36 questionnaire) at 1 year
    - Anxiety, depression
    - Healthcare costs
    - Mortality

Cuthbertson BH et al. A pragmatic randomised, controlled trial of intensive care follow up programmes in improving longer-term outcomes from critical illness. The PRACTICAL study. BMC Health Serv Res 2007 Jul 23; 7: 116.

Disappointing Results



What is already known on this topic

- Critically ill patients who require intensive care have severe and prolonged physical and psychological morbidity, and excess mortality, in the years after discharge from intensive care
- Intensive care follow-up programmes have been developed in an attempt to improve the quality of life of these patients, but evidence for the effectiveness of such programmes is lacking

What this study adds

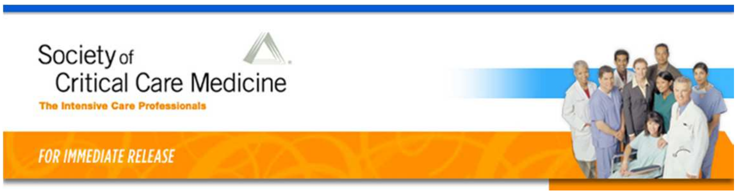
- This pragmatic study showed that nurse led follow-up clinics were neither effective nor cost effective in improving patients' quality of life in the year after their discharge from intensive care
- Use of such follow-up programmes should be reviewed in light of these results

Questions about ICU Recovery Clinics

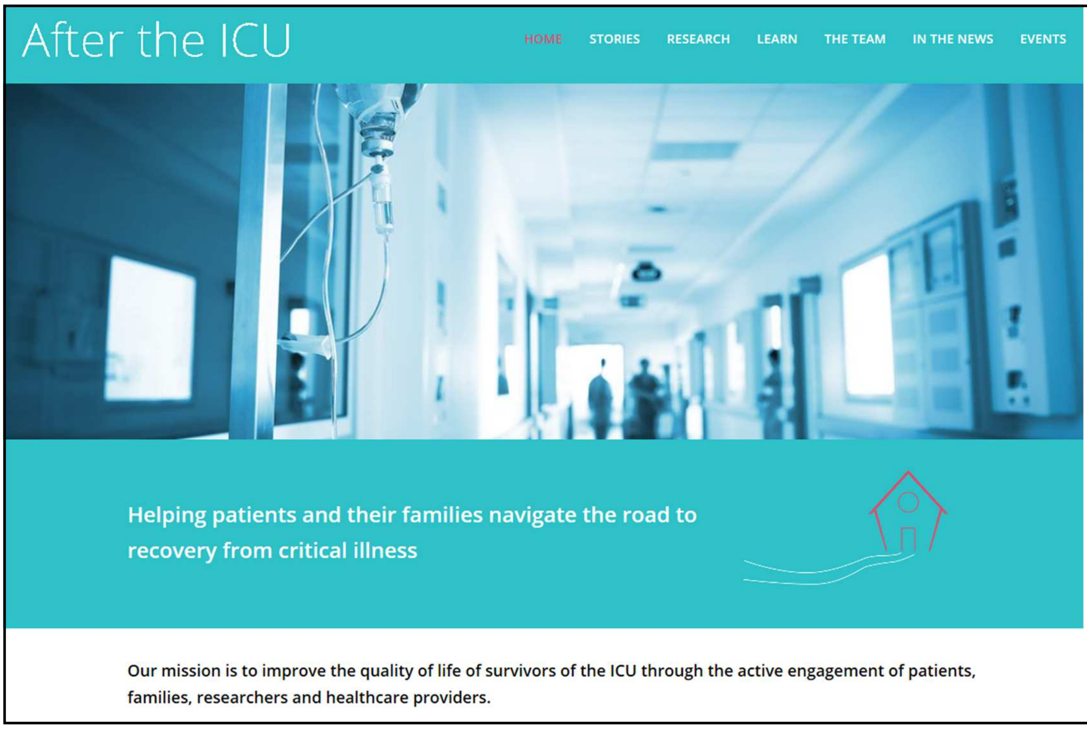
- Are they useful?
- When to intervene? How often?
- Who is likely to get better?

Post ICU Clinics – Our Experience

- At this time, limited referral
- Many want to learn more about what is “normal” post ICU
- Psychiatry and neuropsych referral
- Relief that someone acknowledges their issues


Society of
Critical Care Medicine
The Intensive Care Professionals
FOR IMMEDIATE RELEASE

- SCCM THRIVE Initiative
- ICU Survivor Support Groups at 5 sites around the country and growing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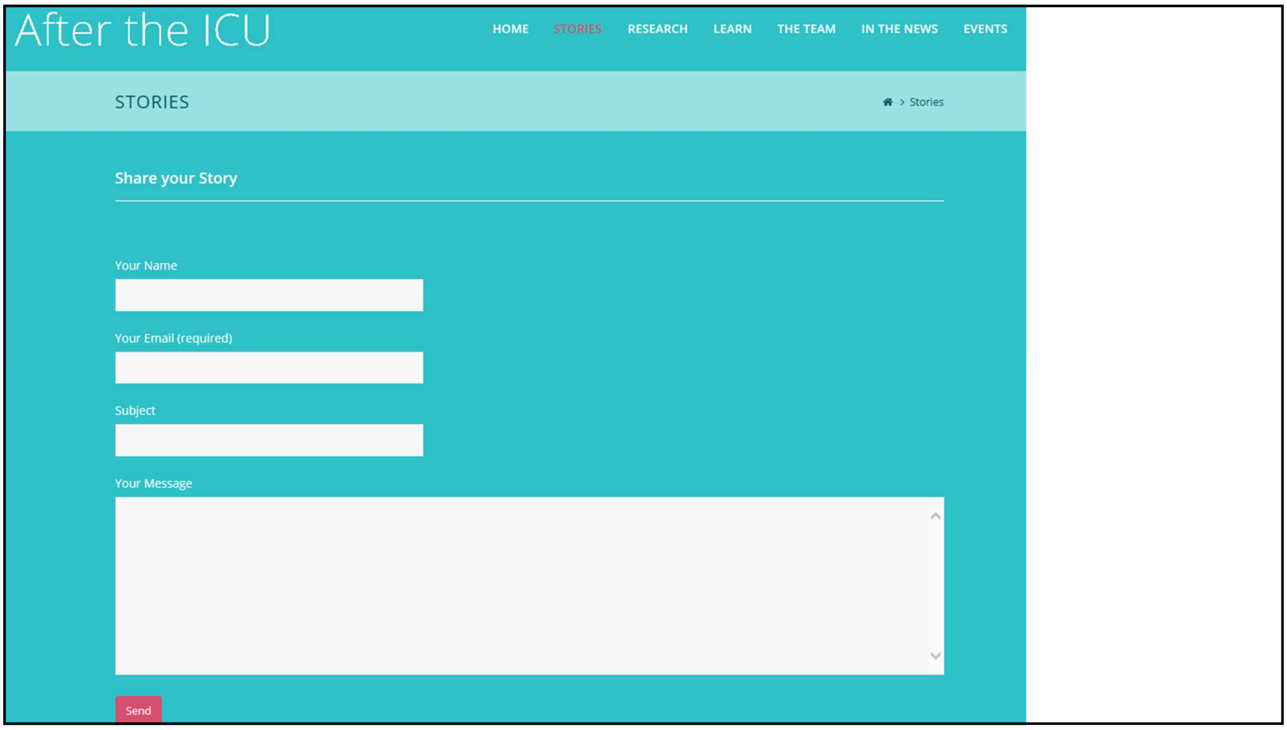
After the ICU

Helping patients and their families navigate the road to recovery from critical illness

Our mission is to improve the quality of life of survivors of the ICU through the active engagement of patients, families, researchers and healthcare providers.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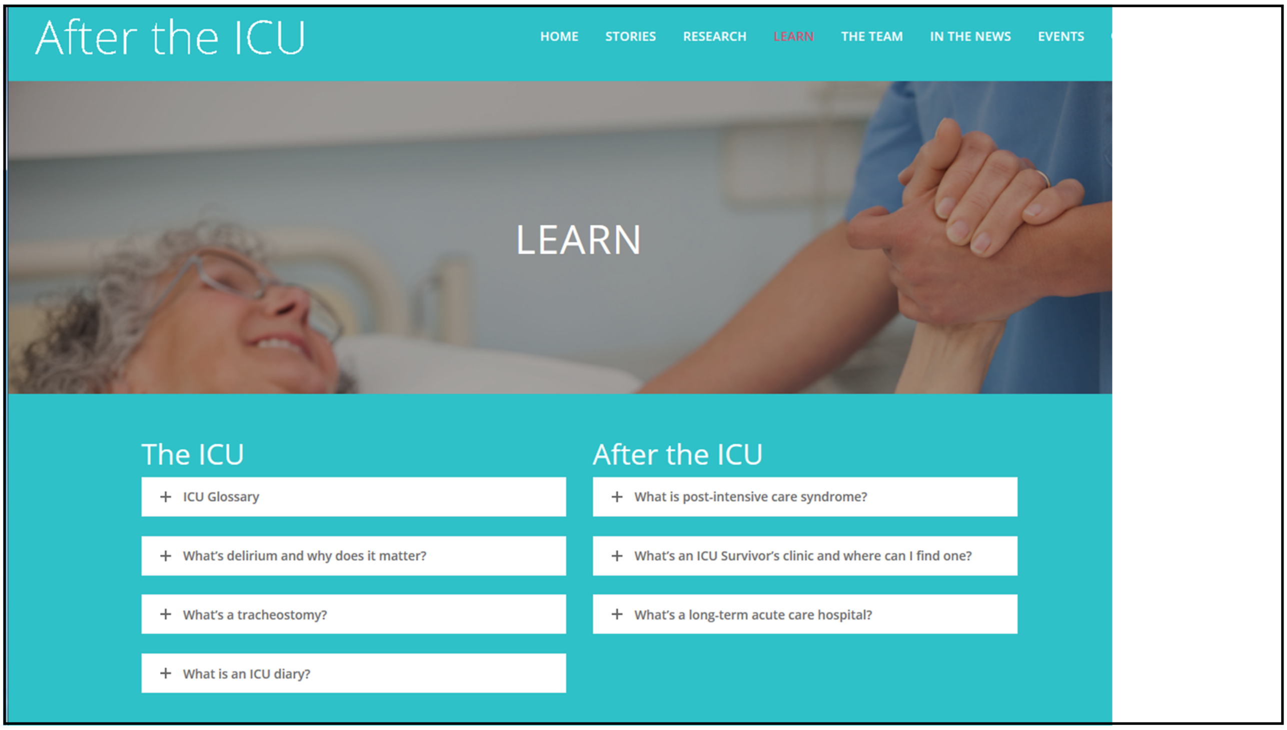
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The ICU

- ICU Glossary
- What's delirium and why does it matter?
- What's a tracheostomy?
- What is an ICU diary?

After the ICU

- What is post-intensive care syndrome?
- What's an ICU Survivor's clinic and where can I find one?
- What's a long-term acute care hospital?

Outline

- Epidemiology
- Post-intensive care syndrome (PICS)
- PICS – Family
- T~~reatment~~? Prevention
- Research and Clinical Efforts

Review Question #1

A patient comes to your clinic. She was recently discharged home after an ICU stay where she was intubated due to respiratory failure from COPD. Which psychiatric problems is she most likely to face as a result of post-intensive care syndrome?

a. Depression, anxiety, post-traumatic stress

b. Psychosis, anxiety, post-traumatic stress

c. Post-traumatic stress, hallucinations, suicidality

d. There are no psychiatric problems that have been associated with intensive care unit admission

Review Question 1 Answer

A patient comes to your clinic. She was recently discharged home after an ICU stay where she was intubated due to respiratory failure from COPD. Which psychiatric problems is she most likely to face as a result of post-intensive care syndrome?

a Depression, anxiety, post-traumatic stress

b. Psychosis, anxiety, post-traumatic stress

c. Post-traumatic stress, hallucinations, suicidality

d. There are no psychiatric problems that have been associated with intensive care unit admission

A systematic review of fourteen studies found the median point-prevalence of “clinically significant” depressive symptoms in ICU survivors to be 28%. A review of the literature for PTSD in ICU survivors examined fifteen studies and found the median point-prevalence of “clinically significant” PTSD symptoms to be 22%. In survivors from the BRAIN-ICU cohort specifically, 37 percent of patients experienced symptoms of depression, which largely seemed to be associated with somatic symptoms.

Review Question #2

What is the burden of cognitive dysfunction in PICS?

a. there is no cognitive dysfunction associated with PICS

b. Around 1/3 of patients a year after critical illness might have cognitive scores similar to those with moderate traumati brain injury

c. 75% of ICU survivors have cognitive dysfunction

d. 10% of ICU survivors have cognitive dysfuncion

Review Question 2 Answer

What is the burden of cognitive dysfunction in PICS?

a. there is no cognitive dysfunction associated with PICS

b. Around 1/3 of patients a year after critical illness might have cognitive scores similar to those with moderate traumati brain injury

c. 75% of ICU survivors have cognitive dysfunction

d. 10% of ICU survivors have cognitive dysfuncion

The BRAIN-ICU study demonstrated the above findings. 24% had cognitive scores similar to those with mild Alzheimer's disease.

Take Home Messages

- We are saving lives
- Things we do in the ICU have long term consequences
- Treatment?

Practice good ICU medicine to have good ICU outcomes
Educate patients/families about PICS
Think of creative ways to impact these problems

References

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UCSD

- Robert Owens, MD (research support and slides)

SCCM THRIVE Initiative

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